

**Tropane Analogs And Methods For
Inhibition of Monoamine Transport**

FIELD OF THE INVENTION

- 5 This invention relates to tropane analogs of cocaine and their use as inhibitors of monoamine reuptake.

BACKGROUND OF THE INVENTION

- Cocaine dependence is a problem of national significance. To date 10 no cocaine pharmacotherapy has been reported. Cocaine is a potent stimulant of the mammalian central nervous system. Its reinforcing properties and stimulant effects are associated with its propensity to bind to monoamine transporters, particularly the dopamine transporter (DAT). (Kennedy, L. T. and I. Hanbauer (1983), *J. Neurochem.* 34: 1137-15 1144; Kuhar, M. J., M. C. Ritz and J. W. Boja (1991), *Trends Neurosci.* 14: 299-302; Madras, B. K., M. A. Fahey, J. Bergman, D. R. Canfield and R. D. Spealman (1989), *J. Pharmacol. Exp. Ther.* 251: 131-141; Madras, B. K., J. B. Kamien, M. Fahey, D. Canfield, et al. (1990), *Pharmacol Biochem. Behav.* 35: 949-953; Reith, M. E. A., B. E. Meisler, 20 H. Sershen and A. Lajtha (1986), *Biochem. Pharmacol.* 35: 1123-1129; Ritz, M. C., R. J. Lamb, S. R. Goldberg and M. J. Kuhar (1987), *Science* 237: 1219-1223; Schoemaker, H., C. Pimoule, S. Arbillia, B. Scatton, F. Javoy-Agid and S. Z. Langer (1985), *Naunyn-Schmiedeberg's Arch. Pharmacol.* 329: 227-235.) It also binds with substantial potency to 25 serotonin transporters (SERT) and norepinephrine transporters.

Structure activity relationship (SAR) studies have largely focused on a series of cocaine analogs. Among the more potent of these congeners at ^3H -cocaine binding sites in striatum (Madras, B. K., M. A. Fahey, J. Bergman, D. R. Canfield and R. D. Spealman (1989), *J. Pharmacol. Exp. Ther.* 251: 131-141; Reith, M. E. A., B. E. Meisler, H. Sershen and A. Lajtha (1986), *Biochem. Pharmacol.* 35: 1123-1129) is (1*R*)-3 β -(4-fluorophenyl)tropane-2 β -carboxylic acid methyl ester, (WIN35,428 or CFT) (Kaufman, M. J. and B. K. Madras (1992), *Synapse*

- 12: 99-111; Madras, B. K., M. A. Fahey, J. Bergman, D. R. Canfield and
R. D. Spealman (1989), *J. Pharmacol. Exp. Ther.* 251: 131-141) reported
in 1973 (Clarke, R. L., S. J. Daum, A. J. Gambino, M. D. Aceto, et al.
(1973), *J. Med. Chem.* 16: 1260-1267). This compound was
5 subsequently radiolabeled to provide a selective probe for the DAT in
primate brain. (Canfield, D. R., R. D. Spealman, M. J. Kaufman and B.
K. Madras (1990), *Synapse* 6: 189-195; Kaufman, M. J. and B. K.
Madras (1991), *Synapse* 9: 43-49; Kaufman, M. J., R. D. Spealman and
B. K. Madras (1991), *Synapse* 9: 177-187.)
10 Among the most potent tropane inhibitors of monoamine binding
sites in striatum are 3 β -(4-(1-methylethenyl)-phenyl)-2 β -propanoyl-8-
azabicyclo(3.2.1)octane and 3 β -(2-naphthyl)-2 β -propanoyl-8-
azabicyclo(3.2.1)octane, (Bennett, B. A., C. H. Wichems, C. K.
Hollingsworth, H. M. L. Davies, C. Thornley, T. Sexton and S. R. Childers
15 (1995), *J. Pharm. Exp. Ther.* 272: 1176-1186; Davies, H. M. L., L. A.
Kuhn, C. Thornley, J. J. Matasi, T. Sexton and S. R. Childers (1996), *J.
Med. Chem.* 39: 2554-2558) (1*R*)-RTI55 (β CIT), (Boja 1991; Boja, J. W., A.
Patel, F. I. Carroll, M. A. Rahman, et al. (1991), *Eur. J. Pharmacol.* 194:
133-134; Neumeyer, J. L., S. Wang, R. A. Milius, R. M. Baldwin, et al.
20 (1991), *J. Med. Chem.* 34: 3144-3146) (1*R*)-RTI121, (Carroll, F. I., A. H.
Lewin, J. W. Boja and M. J. Kuhar (1992), *J. Med. Chem.* 35: 969-981.)
and (1*R*)-3 β -(3,4-di-chlorophenyl)-tropane-2 β -carboxylic acid methyl
ester (O-401), (Carroll, F. I., M. A. Kuzemko and Y. Gao (1992), *Med.
Chem Res.* 1: 382-387; Meltzer, P. C., A. Y. Liang, A.-L. Brownell, D. R.
25 Elmaleh and B. K. Madras (1993), *J. Med. Chem.* 36: 855-862).
SAR studies of the binding of these agents and their effects on
monoamine transporter function have been reported. (Blough, B. E., P.
Abraham, A. H. Lewin, M. J. Kuhar, J. W. Boja and F. I. Carroll (1996), *J.
Med. Chem.* 39: 4027-4035; Carroll, F. I., P. Kotian, A. Dehghani, J. L.
30 Gray, et al. (1995), *J. Med. Chem.* 38: 379-388; Carroll, F. I., A. H.
Lewin, J. W. Boja and M. J. Kuhar (1992), *J. Med. Chem.* 35: 969-981;
Carroll, F. I., S. W. Mascarella, M. A. Kuzemko, Y. Gao, et al. (1994), *J.
Med. Chem.* 37: 2865-2873; Chen, Z., S. Izewasser, J. L. Katz, N. Zhu,

- C. L. Klein and M. L. Trudell (1996), *J. Med. Chem.* 39: 4744-4749; Davies, H. M. L., L. A. Kuhn, C. Thornley, J. J. Matasi, T. Sexton and S. R. Childers (1996), *J. Med. Chem.* 39: 2554-2558; Davies, H. M. L., Z.-Q. Peng and J. H. Houser (1994), *Tetrahedron Lett.* 48: 8939-8942; Davies, H. M. L., E. Saikali, T. Sexton and S. R. Childers (1993), *Eur. J. Pharmacol. Mol. Pharm.* 244: 93-97; Holmquist, C. R., K. I. Keverline-Frantz, P. Abraham, J. W. Boja, M. J. Kuhar and F. I. Carroll (1996), *J. Med. Chem.* 39: 4139-4141; Kozikowski, A. P., G. L. Araldi and R. G. Ball (1997), *J. Org. Chem.* 62: 503-509; Kozikowski, A. P., M. Roberti, L. Xiang, J. S. Bergmann, P. M. Callahan, K. A. Cunningham and K. M. Johnson (1992), *J. Med. Chem.* 35: 4764-4766; Kozikowski, A. P., D. Simoni, S. Manfredini, M. Roberti and J. Stoelwinder (1996), *Tetrahedron Lett.* 37: 5333-5336; Meltzer, P. C., A. Y. Liang, A.-L. Brownell, D. R. Elmalem and B. K. Madras (1993), *J. Med. Chem.* 36: 855-862; Meltzer, P. C., A. Y. Liang and B. K. Madras (1994), *J. Med. Chem.* 37: 2001-2010; Meltzer, P. C., A. Y. Liang and B. K. Madras (1996), *J. Med. Chem.* 39: 371-379; Newman, A. H., A. C. Allen, S. Izenwasser and J. L. Katz (1994), *J. Med. Chem.* 37: 2258-2261; Newman, A. H., R. H. Kline, A. C. Allen, S. Izenwasser, C. George and J. L. Katz (1995), *J. Med. Chem.* 38: 3933-3940; Shreekrishna, V. K., S. Izenwasser, J. L. Katz, C. L. Klein, N. Zhu and M. L. Trudell (1994), *J. Med. Chem.* 37: 3875-3877; Simoni, D., J. Stoelwinder, A. P. Kozikowski, K. M. Johnson, J. S. Bergmann and R. G. Ball (1993), *J. Med. Chem.* 36: 3975-3977.)
- Binding of cocaine and its tropane analogs to monoamine transporters is stereoselective. As example (*1R*)-(-)-cocaine binds at the dopamine transporter about 200-fold more potently than the unnatural isomer, (*1S*)-(+)-cocaine. (Kaufman, M. J. and B. K. Madras (1992), *Synapse* 12: 99-111; Madras, B. K., M. A. Fahey, J. Bergman, D. R. Canfield and R. D. Spealman (1989), *J. Pharmacol. Exp. Ther.* 251: 131-141; Madras, B. K., R. D. Spealman, M. A. Fahey, J. L. Neumeyer, J. K. Saha and R. A. Milius (1989), *Mol. Pharmacol.* 36: 518-524; Reith, M. E. A., B. E. Meisler, H. Sershen and A. Lajtha (1986), *Biochem. Pharmacol.*

35: 1123-1129; Ritz, M. C., R. J. Lamb, S. R. Goldberg and M. J. Kuhar (1987), *Science* 237: 1219-1223.)

Also, only the *R*-enantiomers of cocaine have been found active in a variety of biological and neurochemical measures. (Clarke, R. L., S. J.

- 5 Daum, A. J. Gambino, M. D. Aceto, et al. (1973), *J. Med. Chem.* 16: 1260-1267; Kaufman, M. J. and B. K. Madras (1992), *Synapse* 12: 99-111; Madras, B. K., M. A. Fahey, J. Bergman, D. R. Canfield and R. D. Spealman (1989), *J. Pharmacol. Exp. Ther.* 251: 131-141; Madras, B. K., R. D. Spealman, M. A. Fahey, J. L. Neumeyer, J. K. Saha and R. A. 10 Milius (1989), *Mol. Pharmacol.* 36: 518-524; Reith, M. E. A., B. E. Meisler, H. Sershen and A. Lajtha (1986), *Biochem. Pharmacol.* 35: 1123-1129; Ritz, M. C., R. J. Lamb, S. R. Goldberg and M. J. Kuhar (1987), *Science* 237: 1219-1223; Sershen, H., M. E. A. Reith and A. Lajtha 15 (1980), *Neuropharmacology* 19: 1145-1148; Sershen, H., M. E. A. Reith and A. Lajtha (1982), *Neuropharmacology* 21: 469-474; Spealman, R. D., R. T. Kelleher and S. R. Goldberg (1983), *J. Pharmacol. Exp. Ther.* 225: 509-513.) Parallel stereoselective behavioral effects have also been observed. (Bergman, J., B. K. Madras, S. E. Johnson and R. D. Spealman (1989), *J. Pharmacol. Exp. Ther.* 251: 150-155; Heikkila, R. E., 20 L. Manzino and F. S. Cabbat (1981), *Subst. Alcohol Actions/Misuse* 2: 115-121; Reith, M. E. A., B. E. Meisler, H. Sershen and A. Lajtha (1986), *Biochem. Pharmacol.* 35: 1123-1129; Spealman, R. D., R. T. Kelleher and S. R. Goldberg (1983), *J. Pharmacol. Exp. Ther.* 225: 509-513; Wang, S., Y. Gai, M. Laruelle, R. M. Baldwin, B. E. Scanlet, R. B. Innis and J. L. 25 Neumeyer (1993), *J. Med. Chem.* 36: 1914-1917.) For example, in primates and rodents the stimulating and reinforcing properties of the (-)-enantiomer of cocaine or its 3-aryltropane analogs were considerably greater than for the (+)-enantiomers.

Although SAR studies of cocaine and its 3-aryltropane analogs 30 have offered insight into their mode of binding to monoamine transporters, a comprehensive picture of the binding interaction at the molecular level has not emerged. SAR studies on the classical tropane analogs (Carroll, F. I., Y. Gao, M. A. Rahman, P. Abraham, et al. (1991),

- J. Med. Chem.* 34: 2719-2725; Carroll, F. I., S. W. Mascarella, M. A. Kuzemko, Y. Gao, et al. (1994), *J. Med. Chem.* 37: 2865-2873; Madras, B. K., M. A. Fahey, J. Bergman, D. R. Canfield and R. D. Spealman (1989), *J. Pharmacol. Exp. Ther.* 251: 131-141; Madras, B. K., R. D. Spealman, M. A. Fahey, J. L. Neumeyer, J. K. Saha and R. A. Milius (1989), *Mol. Pharmacol.* 36: 518-524; Meltzer, P. C., A. Y. Liang, A.-L. Brownell, D. R. Elmaleh and B. K. Madras (1993), *J. Med. Chem.* 36: 855-862; Reith, M. E. A., B. E. Meisler, H. Sershen and A. Lajtha (1986), *Biochem. Pharmacol.* 35: 1123-1129) appeared to provide a consistent model for this interaction with the DAT, however, subsequent studies revealed inconsistencies. (Carroll, F. I., P. Kotian, A. Dehghani, J. L. Gray, et al. (1995), *J. Med. Chem.* 38: 379-388; Chen, Z., S. Izewasser, J. L. Katz, N. Zhu, C. L. Klein and M. L. Trudell (1996), *J. Med. Chem.* 39: 4744-4749; Davies, H. M. L., L. A. Kuhn, C. Thornley, J. J. Matasi, T. Sexton and S. R. Childers (1996), *J. Med. Chem.* 39: 2554-2558; Kozikowski, A. P., G. L. Araldi and R. G. Ball (1997), *J. Org. Chem.* 62: 503-509; Meltzer, P. C., A. Y. Liang and B. K. Madras (1994), *J. Med. Chem.* 37: 2001-2010; Meltzer, P. C., A. Y. Liang and B. K. Madras (1996), *J. Med. Chem.* 39: 371-379).
- Carroll had proposed (Boja, J. W., R. M. McNeill, A. Lewin, P. Abraham, F. I. Carroll and M. J. Kuhar (1992), *Mol. Neurosci.* 3: 984-986; Carroll, F. I., P. Abraham, A. Lewin, K. A. Parham, J. W. Boja and M. J. Kuhar (1992), *J. Med. Chem.* 35: 2497-2500; Carroll, F. I., Y. Gao, M. A. Rahman, P. Abraham, et al. (1991), *J. Med. Chem.* 34: 2719-2725; Carroll, F. I., M. A. Kuzemko and Y. Gao (1992), *Med. Chem. Res.* 1: 382-387) four molecular requirements for binding of cocaine and its tropane analogs at the DAT: a 2β -carboxy ester, a basic nitrogen capable of protonation at physiological pH, the *R*-configuration of the tropane and a 3β -aromatic ring at C₃. However, Davies (Davies, H. M. L., E. Saikali, T. Sexton and S. R. Childers (1993), *Eur. J. Pharmacol. Mol. Pharm.* 244: 93-97) later reported that introduction of 2β -ketones did not reduce potency. Kozikowski questioned the role of hydrogen bonding at the C₂ site because introduction of unsaturated and saturated alkyl groups

(Kozikowski, A. P., M. Roberti, K. M. Johnson, J. S. Bergmann and R. G. Ball (1993), *Bioorg. Med. Chem. Lett.* 3: 1327-1332; Kozikowski, A. P., M. Roberti, L. Xiang, J. S. Bergmann, P. M. Callahan, K. A. Cunningham and K. M. Johnson (1992), *J. Med. Chem.* 35: 4764-4766) did not

- 5 diminish binding. Further, the ionic bond between a protonated amine (at physiologically pH) and the presumed (Kitayama, S., S. Shimada, H. Xu, L. Markham, D. H. Donovan and G. R. Uhl (1993), *Proc. Natl. Acad. Sci. U.S.A.* 89: 7782-7785) aspartate residue on the DAT was questioned because reduction of nitrogen nucleophilicity (Kozikowski, A. P., M. K. E. 10 Saiah, J. S. Bergmann and K. M. Johnson (1994), *J. Med. Chem.* 37(37): 3440-3442) by introduction of N-sulfones did not reduce binding potency.

It also has been reported (Madras, B. K., J. B. Kamien, M. Fahey, D. Canfield, et al. (1990), *Pharmacol Biochem. Behav.* 35: 949-953) that introduction of an alkyl or allyl group did not eliminate binding potency.

15 An N-iodoallyl group on the tropane has provided potent and selective ligands for the DAT, and altropine is currently being developed as a SPECT imaging agent (Elmaleh, D. R., B. K. Madras, T. M. Shoup, C. Byon, et al. (1995), *J. Nucl. Chem.*, 37 1197-1202 (1966); Fischman, A. 20 J., A. A. Bonab, J. W. Babich, N. M. Alpert, et al. (1996), *Neuroscience-Net* 1, 00010, (1997). A ^{99m}technetium labeled compound, technepine, which binds potently and selectively to the DAT and provides excellent *in vivo* SPECT images has been reported. (Madras, B. K., A. G. Jones, A. Mahmood, R. E. Zimmerman, et al. (1996), *Synapse* 22: 239-246.)

- 25 (Meltzer, P.C., Blundell, P., Jones, A.G., Mahmood, A., Garada, B. et al., *J. Med. Chem.*, 40, 1835-1844, (1997). 2-Carbomethoxy-3-(bis(4-fluorophenyl)methoxy)tropanes have been reported (Meltzer, P. C., A. Y. Liang and B. K. Madras (1994), *J. Med. Chem.* 37: 2001-2010). The *S*-enantiomer, (*S*)-(+) -2 β -carbomethoxy-3 α -(bis(4- 30 fluorophenyl)methoxy)tropane (Difluoropine) was considerably more potent (IC₅₀: 10.9 nM) and selective (DAT v. SERT: 324) than any of the other seven isomers, including the *R*-enantiomers.

Drug therapies for cocaine abuse are needed. Also, there is a need for protective agents for neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease as well as therapeutic agents for dopamine related dysfunction such as Attention Deficit Disorder.

- 5 Compounds that inhibit monoamine reuptake in the mammalian system are sought to provide such therapies.

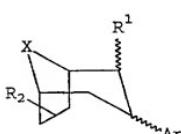
Inhibition of 5-hydroxytryptamine reuptake has an effect on diseases mediated by 5HT receptors. Compounds that provide such inhibition can be useful, for example, as therapeutic anti-depressants.

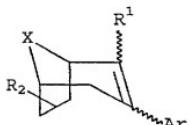
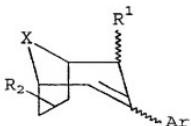
- 10 Cocaine recognition sites are localized on monoamine transporters such as, for example, the dopamine transporter (DAT) and serotonin transporter (SERT). These transporters are localized, in turn, on monoamine nerve terminals. Compounds that bind to these sites can be useful as (i) probes for neuro-degenerative diseases (e.g., Parkinson's disease), (ii) therapeutic drugs for neurodegenerative diseases (e.g., Parkinson's and Alzheimer's disease), (iii) therapeutic drugs for dopamine dysfunction (e.g., Attention Deficit Disorder), (iv) treatment of psychiatric dysfunction (e.g., depression) and (v) treatment of clinical dysfunction (e.g., migraine).
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20 SUMMARY OF THE INVENTION

The compounds of this invention are new tropane analogs that bind to monoamine transporters. Thus, the present invention provides tropane analogs having one of the following formula:

25





5 wherein:

R₁ = COOR₇, COR₃, lower alkyl, lower alkenyl, lower alkynyl, CONHR₄, or COR₆ and is α or β ;

R₂ = OH or O, is a 6- or 7- substituent, and if R₂ is OH, it is α or β ;

X = NR₃, CH₂, CHY, CYY₁, CO, O, S; SO, SO₂, NSO₂R₃, or C=CX₁Y

10 with the N, C, O or S atom being a member of the ring:

X = NR₃, CH₂, CHY, CYY₁, CO, O, S; SO, SO₂, or NSO₂R₃;

R₃ = H, (CH₂)_nC₆H₄Y, C₆H₄Y, CHCH₂, lower alkyl, lower alkenyl or lower alkynyl;

Y and Y₁ = H, Br, Cl, I, F, OH, OCH₃, CF₃, NO₂, NH₂, CN,

15 NHCOCH₃, N(CH₃)₂, (CH₂)_nCH₃, COCH₃, or C(CH₃)₃;

R₄ = CH₃, CH₂CH₃, or CH₃SO₂;

R₆ = morpholinyl or piperidinyl;

Ar = phenyl-R₅, naphthyl-R₅, anthracenyl-R₅, phenanthrenyl-R₅, or diphenyloxymethoxy-R₅;

20 R₅ = H, Br, Cl, I, F, OH, OCH₃, CF₃, NO₂, NH₂, CN, NHCOCH₃, N(CH₃)₂, (CH₂)_nCH₃, COCH₃, C(CH₃)₃ where n= 0-6, 4-F, 4-Cl, 4-I, 2-F, 2-Cl, 2-I, 3-F, 3-Cl, 3-I, 3,4-diCl, 3,4-diOH, 3,4-diOAc, 3,4-diOCH₃, 3-OH-4-Cl, 3-OH-4-F, 3-Cl-4-OH, 3-F-4-OH, lower alkyl, lower alkoxy, lower alkenyl, lower alkynyl, CO(lower alkyl), or CO(lower alkoxy);

25 n = 0, 1, 2, 3, 4 or 5;

R₇= lower alkyl; and

when X = N, R₁ is not COR₅.

The substituents at the 2 and 3 position of the ring can be α- or β. Although R₁ is illustrated in the 2- position, it should be recognized that substitution at the 4- position is also included and the position is dependent on the numbering of the tropane ring. The compounds of the present invention can be racemic, pure *R*-enantiomers, or pure *S*-enantiomers. Thus, the structural formulas illustrated herein are intended to represent each enantiomer and diastereomer of the illustrated compound. In certain preferred compounds of the present invention, R₁ is COOCH₃. In yet other preferred compounds, R₁ is COR₃, where R₃ is CHCH₂. Other preferred compounds are 6 or 7-bridge hydroxylated or keto compounds

The compounds of the present invention can be radiolabelled, for example, to assay cocaine receptors. Certain preferred compounds of the present invention have a high selectivity for the DAT versus the SERT. Preferred compounds have an IC₅₀ SERT/DAT ratio of greater than about 10, preferably greater than about 30 and more preferably 50 or more. In addition, preferably the compounds have an IC₅₀ at the DAT of less than about 500 nM, preferably less than 60 nM, more preferably less than about 20, and most preferably less than about 10.

The present invention also provides pharmaceutical therapeutic compositions comprising the compounds formulated in a pharmaceutically acceptable carrier.

Further, the invention provides a method for inhibiting 5-hydroxytryptamine reuptake of a monoamine transporter by contacting the monoamine transporter with a 5-hydroxy-tryptamine reuptake inhibiting (5-HT inhibiting) amount of a compound of the present invention. Inhibition of 5-hydroxy-tryptamine reuptake of a monoamine transporter in a mammal is provided in accord with the present invention by administering to the mammal a 5-HT inhibiting amount of a compound of the present invention in a pharmaceutically acceptable carrier. Preferred monoamine transporters for the practice of the present

invention include the dopamine transporter, the serotonin transporter and the norepinephrine transporter.

In a preferred embodiment, the invention also provides a method for inhibiting dopamine reuptake of a dopamine transporter by
5 contacting the dopamine transporter with a dopamine reuptake inhibiting amount of a compound of the present invention. Inhibition of dopamine reuptake of a dopamine transporter in a mammal is provided in accord with the present invention by administering to the mammal a dopamine inhibiting amount of a compound of the present invention in a
10 pharmaceutically acceptable carrier.

The invention also relates to a method for treating a mammal having a disorder selected from neurodegenerative disease, psychiatric dysfunction, dopamine dysfunction, cocaine abuse and clinical dysfunction comprising administering to the mammal an effective amount of a compound of the present invention. In preferred methods, the compound has a 3α -group. In certain methods, the neurodegenerative disease is selected from Parkinson's disease and Alzheimer's disease. An example of a psychiatric disorder which can be treated by the present methods is depression.

20 The invention also relates to methods for treating dopamine related dysfunction in a mammal comprising administering to the mammal a dopamine reuptake inhibiting amount of a compound as described herein. In preferred methods, the compound is a boat tropane. An example of a dopamine related dysfunction is Attention deficit
25 disorder.

The term "lower alkyl" when used herein designates aliphatic saturated branched or straight chain hydrocarbon monovalent substituents containing from 1 to about 8 carbon atoms such as methyl, ethyl, isopropyl, n-propyl, n-butyl, $(CH_2)_nCH_3$, $C(CH_3)_3$; etc., more preferably 1 to 4 carbons. The term "lower alkoxy" designates lower alkoxy substituents containing from 1 to about 8 carbon atoms such as methoxy, ethoxy, isopropoxy, etc., more preferably 1 to 4 carbon atoms.

The term "lower alkenyl" when used herein designates aliphatic unsaturated branched or straight chain vinyl hydrocarbon substituents containing from 2 to about 8 carbon atoms such as allyl, etc., more preferably 2 to 4 carbons. The term "lower alkynyl" designates lower alkynyl substituents containing from 2 to about 8 carbon atoms, more preferably 2 to 4 carbon atoms such as, for example, propyne, butyne, etc.

5 The terms substituted lower alkyl, substituted lower alkoxy, substituted lower alkenyl and substituted lower alkynyl, when used
10 herein, include corresponding alkyl, alkoxy, alkenyl or alkynyl groups substituted with halide, hydroxy, carboxylic acid, or carboxamide groups, etc. such as, for example, -CH₂OH, -CH₂CH₂COOH, -CH₂CONH₂, -OCH₂CH₂OH, -OCH₂COOH, -OCH₂CH₂CONH₂, etc. As used herein, the terms lower alkyl, lower alkoxy, lower alkenyl and lower alkynyl are
15 meant to include where practical substituted such groups as described above.

20 When X contains a carbon atom as the ring member, reference to X is sometimes made herein as a carbon group. Thus, when X is a carbon group, as that phrase is used herein, it means that a carbon atom is a ring member at the X position (i.e., the 8- position).

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 illustrates the structures of Lead Bicyclo{3.2.1}octanes.

FIGURE 2 illustrates the absolute Configurations of (1*R*)-8a, (1*R*-

25 18a, (1*S*)-18a.

FIGURE 3 illustrates a reaction scheme (Scheme 1) for the preparation of 2,3-Unsaturated Tropanes.

FIGURE 4 illustrates a reaction scheme (Scheme 2) for the preparation of Bridge Oxygenated Tropanes.

30 FIGURE 5 illustrates a reaction scheme (Scheme 3) for the preparation of Bridge Oxygenated 2-Keto Tropanes.

FIGURE 6 illustrates a reaction scheme (Scheme 4) for the resolution of 8a, 15a and 18a.

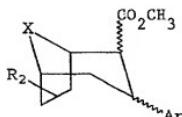
FIGURE 7 illustrates a reaction scheme (Scheme 5) for the inversion at C6 and C7.

FIGURE 8 illustrates a reaction scheme (Scheme 6) for the preparation of Diarylmethoxy Tropanes.

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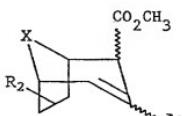
DETAILED DESCRIPTION OF THE INVENTION

In accord with the present invention, novel tropane compounds are provided that bind to monoamine transporters, preferably the DAT. Certain preferred compounds also have a high selectivity for the DAT versus the SERT. The tropane analogs of the present invention have hydroxyl or ketone substituents in the 6- or 7- position of the tropane structure. Preferred compounds of the invention include those having the formula:

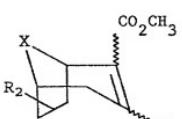


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or

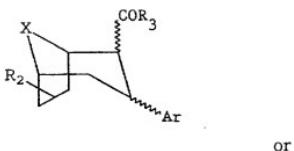


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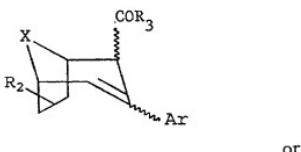


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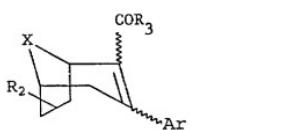
Other preferred compounds have the following formula:



or



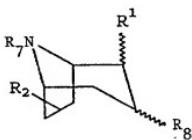
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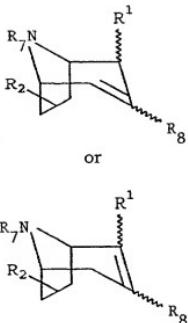
Particularly preferred compounds have X includes a nitrogen, carbon or oxygen atom as a ring member, R₂ is OH, and Ar is phenyl, substituted phenyl such as mono- or di-halogen substituted phenyl, or a diarylmethoxy including halogen substituted such groups.

- 10 The invention also relates to compounds having the structural formula:



or

15



5

wherein:

$R_1 = COOR_7, COR_3$, lower alkyl, lower alkenyl, lower alkynyl,

CONHR_4 , $\text{CON}(\text{R}_7)\text{OR}_7$ or COR_6 and is α or β ;

$R_2 = OR_3$ and is a 6- or 7- substituent;

10 R₃= H, (CH₂)_nC₆H₄Y, C₆H₄Y, CHCH₂, lower alkyl, lower alkenyl or

$R = \text{CH}_2 - \text{CH}(\text{CH}_3)_2$ or $\text{CH}_2\text{-SO}_2\text{C}_6\text{H}_4\text{CH}_3$

REFERENCES

R_3 = naphthoxy, phenoxyl, R_4 = naphthyl, R_5 = anthracenyl, R_6 =

15. *Chemical and Physical Properties*

R = H, F, Cl, Br, OH, OCH₃, CF₃, NO₂, NH₂, CN, NHCOCH₃.

$N(CH_3)_2$, $(CH_2)nCH_3$, $COCH_3$, $C(CH_3)_3$ where $n=0-6$, 4-F, 4-Cl, 4-I, 2-F, 2-Cl, 2-I, 3-F, 3-Cl, 3-I, 3,4-diCl, 3,4-diOH, 3,4-diOAc, 3,4-diOCH₃, 3-OH-4-Cl, 3-OH-4-F, 3-Cl-4-OH, 3-F-4-OH, lower alkyl, lower alkoxy, lower

20 alkenyl, lower alkynyl, CO(lower alkyl), or CO(lower alkoxy);

$n = 0, 1, 2, 3, 4$ or 5 ;

R_7 = lower alkyl; and R_8 = a protecting group.

Examples of suitable groups for use as R₂ in these embodiments which comprise a protecting group include substituted methyl ethers where R₉ = -CH₃; -CH₂OCH₃; -CH₂OCH₂C₆H₅; -CH₂OCH₂C₆H₄-4-OCH₃; -CH₂OCH₂C₆H₄-4-OCH₃; -CH₂OC(CH₃)₃; -CH₂OSi(C₆H₅)₂C(CH₃)₃; -CH₂OSi(CH₃)₂C(CH₃)₃; -CH₂OCH₂CH₂OCH₃; -CH-CH₂CH₂CH₂CH₂O-

(tetrahydropyranylether). Other examples of suitable groups for use as R₂ include substituted ethyl ethers where R₉ = -CH(OC₂H₅)CH₃; -C(OCH₂C₆H₅)(CH₃)₂; -CH₂CCl₃; -CH₂CH₂Si(CH₃)₃; -C(CH₃)₃; -CH₂CH=CH₂; -C₆H₄-4-Cl; -C₆H₄-4-OCH₃; -C₆H₃-2,4-(NO₂)₂; -CH₂C₆H₅. It can also

5 include substituted benzyl ethers, where such as R₉ = -CH₂C₆H₄-4-OCH₃; -CH₂C₆H₃-3,4-(OCH₃)₂; -C(C₆H₅)₂C₆H₄-4-OCH₃ or silyl ethers, where R₉ = -Si(CH₃)₃; -Si(CH₂CH₃)₃; -Si(CH(CH₃)₂)₃; -Si(CH₃)₂(CH(CH₃)₂); -Si(CH₃)₂C(CH₃)₃; -Si(C₆H₅)₂C(CH₃)₃. R₂ can include esters, where R₉ = -CHO; -COCOC₆H₅; -COCH₃; -camphanyl; -COC₆H₅ or also carbonates where R₉ = -COOCH₃; -COOCH₂CH₃; -COOCH₂CCl₃; -COOCH=CH₂; -COOCH₂CH=CH₂; -COOCH₂C₆H₅; -COOCH₂C₆H₄-4-C. One of ordinary skill in the art can readily select an appropriate protecting group. These compounds in this group are useful as intermediates in obtaining the 6- and 7-hydroxylated tropanes of the present invention. In certain

10 preferred embodiments, R₁ is selected from COOR₇, COR₃, or CON(R₇)OR₇; R₃ is lower alkyl; R₈ is camphanoyl or phenyl-R₅; R₇ is CH₃ and R₆ is MOM.

The 6- and 7-hydroxylated tropanes of the present invention have similar potency to their unsubstituted counterparts but unexpectedly manifest greater selectivity for the DAT. SAR in this series mimics that found in other tropanes in which 3,4-dichloro substitution generally confers greatest potency at the DAT and the unsubstituted phenyl ring at C3 is least potent. The 7-Hydroxylated compounds of the present invention are more potent at the DAT than the 6-hydroxylated counterparts. In accord with known SAR, the 3*a*-aryl compounds of the present invention manifest a marked selectivity for DAT inhibition. As for other tropanes, the DAT has been found to be enantioselective and the 1*S*-isomers of the compounds of the present invention are considerably more potent inhibitors than the 1*R* enantiomers. Finally, introduction of a C2-ethylketone in the present compounds, e.g. Compound 26, provides extremely potent and selective DAT inhibitors.

The route of synthesis is shown in Schemes 1, 2 and 3. The 6- and 7-hydroxy target compounds were obtained individually, however,

for ease of presentation, the position of bridge substitution is not specified in the schemes. The 6- and 7- hydroxy β -keto esters **1a** and **1b** were prepared as described previously (Chen, Z.; Meltzer, P. C., *Tetrahedron Lett.* 1997, 38, 1121-1124; Robinson, R., *J. Chem. Soc.*

- 5 1917, 111, 762; Nedenskov, P.; Clauson-Kaas, N., *Acta Chem. Scand.* 1957, 22, 1385; Sheehan, J. C.; Bloom, B. M., *J. Am. Chem. Soc.* 1952, 74, 3825). The stereochemistry of the β -hydroxyl group at C6 (**1a**) or C7 (**1b**) was confirmed by NMR studies. Most important, a coupling constant of $J = 0$ Hz between H-5 and H-6 ($\delta = 4.05$ ppm) in the case of **1a**, and 10 between H-1 and H-7 ($\delta = 4.1$ ppm) in the case of **1b**, confirmed a dihedral angle of 90° for both compounds. This dihedral angle can only be obtained between a 6 α - or 7 α -oriented proton and the relevant bridgehead proton at C1 or C5 respectively. This therefore confirms the β -orientation of the hydroxy moieties in **1a** and **1b**. No α -hydroxy isomers 15 were isolated.

A mixture of 6- and 7- hydroxy- β -keto esters **1a** and **1b** was methoxymethylated with dimethoxymethane in dichloromethane with *p*-toluenesulfonic acid as catalyst. Column chromatography provided regiosomers **2a** and **2b** which were individually utilized, as described below. The ^1H NMR spectra of **2a** and **2b**, as well as pure **1a** and **1b**, proved quite interesting. Both compounds **1a** and **2a** clearly exhibit the expected (Meltzer, P. C. et al., *J. Med. Chem.* 2000, 43, 2982-2991) equilibrium distribution between the 2 α -carboxy ester, enol-2-carboxy ester, and 2 β -carboxy ester with the result that their ^1H NMR spectra are quite complex. Compounds **1b** and **2b** surprisingly do not. In fact, in CDCl_3 solution, compounds **1b** and **2b** exist exclusively as the enol. Unequivocal evidence for this lies (as exemplified for **1b**) in the complete absence of a C2 proton and the presence of a doublet at δ 1.73 ($\text{H}_{4\beta}$; $J = 18.6$ Hz) and a double doublet at δ 2.76 ($\text{H}_{4\alpha}$; $J = 18.6$ and 4.7 Hz) 25 integrating for fully one proton each. The enolic proton at δ 11.8 also fully integrates for one proton. The reason for this preference for the enol in the 7-substituted compounds is unclear.

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Conversion of **2** to the vinyl enoltriflates **3** was achieved with sodium bis(trimethylsilyl)amide and *N*-phenyltrifluoromethanesulfonimide at low temperature (Keverline, K. I. et al., *Tetrahedron Lett.* 1995, **36**, 3099-3102). The alkenes **4** and **5** were then obtained in good yield by Suzuki coupling (Oh-e, T. et al., *J. Org. Chem.* 1993, **58**, 2201-2208) of the triflates **3** with the corresponding boronic acids. Reduction of **4** and **5** (Scheme 2) with samarium iodide at -78 °C then afforded the saturated tropane analogs **9-12** (Keverline, K. I. et al., *Tetrahedron Lett.* 1995, **36**, 3099-3102). Compounds **9** and **11** were shown by ¹H NMR to exist in a chair conformation, and **10** and **12** assumed a boat conformation. Finally, the MOM groups of each of **4**, **5** and **9-12** were removed in high yield with trimethylsilyl bromide in methylene chloride at 0 °C to give the corresponding hydroxy tropanes **7** and **8** (Scheme 1), **14** and **15**, and **17** and **18** (Scheme 2) respectively.

The 7-ketoesters **19** and **20** were obtained in good yield upon oxidation of **15** and **18** respectively with tetra-*n*-propylammonium perruthenate (Griffith, W. P. et al., *J. Chem. Soc. Chem. Commun.* 1987, **21**, 1625-1627) and *N*-methylmorpholine-N-oxide in methylene chloride.

The 2-ethylketone analogs **23** and **26** were prepared (Scheme 3) via an intermediate Weinreb amide (Basha et al., *Tet. Lett.* 1977, **48**, 4171-4174). Thus **11a** was reacted with *N,O*-dimethylhydroxylamine and trimethyl aluminum in methylene chloride to provide the Weinreb amide **21** in high yield. Treatment with ethyl magnesium bromide in THF (Evans, D. A. et al., *J. Amer. Chem. Soc.* 1998, **120**, 5921-5942) then provided the ethyl ketone **22** quantitatively. Deprotection with TMSBr yielded the target compound **23**. The 3α-aryl analog **26** was obtained similarly from **12a** via **24** and **25**.

In order to determine the biological enantioselectivity of these hydroxytropanes, six enantiopure 7β-hydroxy-3-(3,4-dichlorophenyl) analogs were prepared. While we and others (Findlay, S. P., *J. Org. Chem.* 1957, **22**, 1385-1393; Carroll, F. I. et al., *J. Med. Chem.* 1991, **34**, 883-886; Meltzer, P. C. et al., *J. Med. Chem.* 1994, **37**, 2001-2010) have had substantial success in recrystallization of diastereomeric tartrate salts of

keto esters such as **1b**, we were unable to obtain material of satisfactory enantiomeric excess (ee) with the bridge hydroxyl group present. We therefore elaborated two resolution routes, both of which relied upon the establishment of diastereomeric camphanate esters (Scheme 4). The

routes had the added advantage of allowing quantification of ee by ¹H NMR analysis (*vide infra*). Thus, the MOM protected keto ester **2b** was reacted with (1'S)-(-)-camphanic chloride to obtain a mixture of diastereomers that could not be separated by column chromatography. Multiple recrystallizations yielded a sufficient amount of the (1R,1'S) diastereomer **27** only. Pure (1S,1'S) diastereomer could not be obtained by these means. Hydrolysis of **(1R)-27** with lithium hydroxide then provided enantiopure keto ester **(1R)-2**. This keto ester was then taken through the same synthetic pathway as shown for racemates **1b** (Schemes 1 and 2) to obtain the enantiopure **(1R)-8a**, **(1R)-15a**, and **(1R)-18a**.

This approach provided only the 1R-tropanes. Therefore an alternate approach was also developed. (Scheme 4). The racemic 2,3-ene **8a** was esterified with (1'S)-(-)-camphanic chloride to obtain a diastereomeric mixture **28** which was purified by column chromatography to obtain **(1S,1'S)-28**. Hydrolysis with LiOH then provided the enantiopure target compound **(1S)-8a** which was reduced with SmI₂ to obtain the 3β **(1S)-15a** and 3α **(1S)-18a** target compounds. Physical data relating to these six compounds are presented in Table 1.

Table 1. Physical Data for Six Enantiopure Analogs

Compound	Mp °C	X-ray ^a	$[\alpha]^{25}_{D}$
(1R)-8a	129.0-131.0	(1R)	+57°
(1R)-15a	186.0-187.0		-26°
(1R)-18a	149.0-150.0	(1R)	+47°
(1S)-8a	130.4-132.4		-58°
(1S)-15a	185.5-186.5		+25°
(1S)-18a	148.5-150.0	(1S)	-48°

^a X-ray crystallographic analysis confirmed stereochemical assignments

Each enantiomeric pair had equal and opposite optical rotations. Since this is an unreliable measure of enantiomeric excess, an NMR method was developed. Each of the six compounds was obtained in >98% ee as confirmed by ¹H NMR. In this regard, NMR spectra of the

- 5 camphanate esters are unequivocal since one of the camphanate methyl resonances for the (1*R*,1'S) and (1*S*,1'S) compounds is base-line separated and can therefore be quantified reliably. Thus the (1*R*)-**27** manifests a methyl group at δ 0.99. The (1*S*)-**27** shows the same methyl at δ 1.02. Absolute stereochemistry was assigned by X-ray
10 crystallographic analysis for (1*R*)-**8a**, (1*R*)-**18a**, and (1*S*)-**18a**. This allowed confident stereochemical assignment of the remaining compounds.

It should be noted that the designation of chirality for these bridge-hydroxylated tropanes is reversed from that of the bridge unsubstituted parent compounds. This is a result of the rules for nomenclature and does not reflect a difference in absolute stereochemistry. Thus the more potent enantiomers here are the 1*S* designated compounds in contrast to the 1*R* active enantiomers of the parent compounds **6a**, **13a**, or **16a**.

- 20 Inversion of the bridge hydroxyl group in **17a** and **18a** was effected (Scheme 5) in two steps by straightforward Mitsunobu chemistry (Mitsunobu, O., *Synthesis* 1981, 1-28). Thus the 6 β -hydroxy **17a** was reacted with benzoic acid and triphenylphosphine in the presence of diethylazodicarboxylate to give **29a**. The benzoyl group was then removed
25 with LiOH/THF to provide the 6 α -hydroxy analog **30a**. The 7 β -hydroxy analog **18a** was treated similarly to obtain **30b**.

- The ¹H NMR spectra of these inverted compounds are interesting in that the α -oriented hydroxyls have a surprisingly large through space compression effect on the axial protons at H2 α in the case of the 7-OH compound **30b** and at H4 α in the case of the 6 α -hydroxy compound **30a**. Such effects have been observed previously in epibatidine analogs (Fletcher, S. R. et al., *J. Org. Chem.* 1994, 59, 1771-1778). Boat versus chair conformation of bicyclo{3.2.1}octanes has always been assigned on

the basis of ^1H NMR, and the signal corresponding to H 4α in 2 β -substituted-3 α -aryl bicyclo[3.2.1]octanes has been particularly diagnostic. It generally appears as a double doublet at δ 1.3 showing large geminal coupling interactions with H 4β (ca. 14 Hz) and H 3 (trans-diaxial coupling ca. 11 Hz) and a small coupling constant with H 5 (ca. 2 Hz). That is the case for the 2 β -carbomethoxy-3 α -(3,4-dichlorophenyl) hydroxylated derivatives when the hydroxyl group is in the 6 β (**17a**), 7 β (**18a**), or 7 α (**30b**) orientation (in the latter case obscured by the presence of a signal corresponding to H 6β). In the case of the 6 α -hydroxy derivative **30a**, the signal corresponding to H 4α was observed at δ 2.15 (Δ = 0.85 ppm) (with the appropriate multiplicity described above) due to the strong 1,4-diaxial interaction with the 6 α -OH. A similar displacement (Δ = 0.9 ppm) was observed in the signal corresponding to H 2α in the 7 α -hydroxy compound, **30b**. Finally the ^1H NMR spectrum of the 7-keto compound **20** showed a strong resemblance with the hydroxy analog's spectra, although the signal corresponding to H 4α appeared at lower fields (δ 1.51) and the trans-diaxial coupling interactions H 3 -H 2 and H 3 -H 4α were slightly weaker than expected (J = 8 Hz). These minor differences indicate a pseudo boat conformation.

The diarylmethoxy compounds (Scheme 6) **32a** and **32b** were obtained from the MOM protected keto esters **1a** and **1b**. Reduction with sodium borohydride gave the 3 α -hydroxy compounds **31**. Subsequent reaction with 4,4'-difluorobenzhydrol in methylene chloride with *p*-toluenesulfonic acid provided **32a** or **32b** directly.

In order to assign absolute stereochemistry for those compounds that were prepared in enantiomerically pure form, X-ray structural analyses were conducted. Compounds (**1R**)-**8a**, (**1R**)-**18a**, and (**1S**)-**18a** were recrystallized from methylene chloride/pentane to obtain suitable crystals. Compound (**1S**)-**18a** was thus demonstrated to be the **1S**-enantiomer. Compound (**1R**)-**18a** was proved to be **1R**, and compound (**1R**)-**8a**, the precursor to (**1R**)-**18a**, was likewise confirmed as **1R** (Figure 2). A comparison of the conformation established by ^1H NMR studies in

solution (CDCl_3) with that evident in the solid state as evidenced by X-ray crystallography proved interesting. While both 3α -aryl enantiomers adopted a boat conformation in solution, the $1R$ enantiomer **(1R)-18a** presented in chair conformation in the solid state. Among the numerous X-ray crystallographic structural determinations that we have conducted on tropanes, **(1R)-18a** represents the first instance in which the conformation in the solid state is markedly different from that in solution. This is highly unlikely to be a consequence of enantiomeric differences (**(1R)-18a** vs. **(1S)-18a**). However, this difference is potentially important since a chair conformation would place the 3α -aryl substituent in an axial position. SAR studies have taken into consideration that a 3β -substituent, which favors the chair conformation of the bicyclo[3.2.1]octane system, places the 3α -aryl group in an equatorial position. Further, the 3α -aryl compounds have, on the basis of NMR studies and all prior X-ray studies, been shown to adopt a boat conformation in which the C3-aryl group is again oriented equatorially. This contrast between the crystal conformation of **(1S)-18a** (boat) as compared with that of its enantiomer **(1R)-18a** (chair) is probably fortuitous. It was noted that the unit cell structures for **(1R)-18a** and **(1S)-18a** differed with respect to intermolecular hydrogen bonding. It appeared that **(1S)-18a** manifested H-bonding between the 7-OH and the 7-OH of an adjacent molecule, while **(1R)-18a** manifested H-bonding between a 7-OH and an 8-N of an adjacent molecule. ^1H NMR experiments were conducted to examine the possible influence of such intermolecular hydrogen bonding upon conformation. The conformation of the 3α -molecule **(1S)-18a** in CDCl_3 solution is pseudo-boat (evidenced by the double doublet resonances for $\text{H}_{4\alpha}$ at δ 1.24). It maintains this conformation in $\text{CD}_3\text{OD}/\text{D}_2\text{O}$ ($\text{H}_{4\alpha}$: ddd at δ 1.3) or $\text{CD}_3\text{OD}/\text{H}_2\text{O}$ ($\text{H}_{4\alpha}$: ddd at δ 1.3) under a water suppression protocol. Therefore intermolecular hydrogen bonding does not favor chair conformation over the boat for this compound. This result highlights the caution that should be exercised as one extrapolates from a three dimensional crystal structure to a putative three-dimensional structure within the biological system.

The affinities (IC_{50}) for the dopamine and serotonin transporters were determined in competition studies. The dopamine transporter was labeled with [^3H]3 β -(4-fluorophenyl)tropane-2 β -carboxylic acid methyl ester ([^3H]WIN 35,428 or [^3H]CFT (1 nM)) and non-specific binding was measured with (-)-cocaine (30 μM) (Madras, B. K. et al., *J. Pharmacol.*

5 *Exp. Ther.* 1989, 251, 131-141). [^3H]Citalopram was used to label the serotonin transporter and non-specific binding was measured with fluoxetine(10 μM) (Madras, B. K. et al., *Synapse* 1996, 24, 340-348).

10 Binding data for the 2-carbomethoxy-6- or 7-hydroxy compounds are presented in Table 2. Table 2 shows the inhibition of [^3H]WIN 35,428 binding to the dopamine transporter and [^3H]citalopram binding to the serotonin transporter in rhesus (*macaca mulata*) or cynomolgus monkey (*macaca fascicularis*) caudate-putamen. Each value is the mean of 2 or more independent experiments each conducted in different brains and in 15 triplicate. Errors generally do not exceed 15% between replicate experiments. Highest doses tested were generally 10-100 μM .

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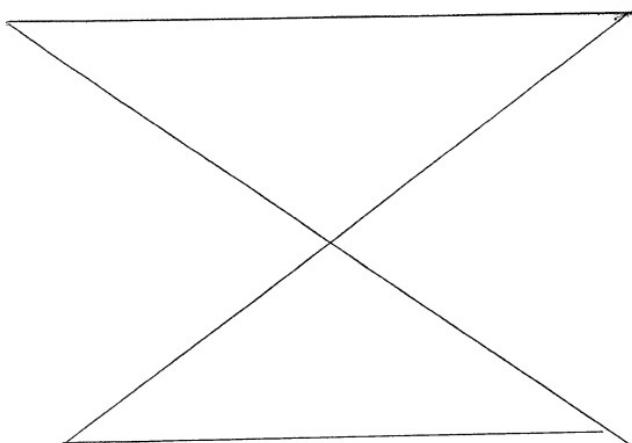
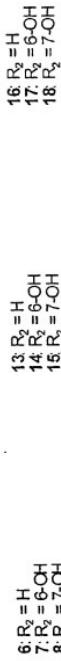
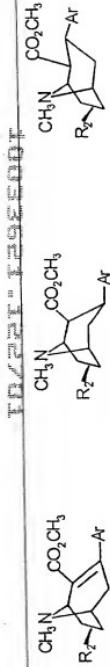


Table 2.



Ar: a = 3,4-Cl₂ phenyl b = 2-Naphthyl c = 4-F-phenyl d = Phenyl

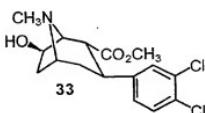


R ₂	Compound	DAT	SERT	SERT/DAT	Compound	DAT	SERT	SERT/DAT	Compound	DAT	SERT	SERT/DAT
H	6a, O-1109	1.16	867	747	13a, O-401 (R)	1.09	2.47	2	16a, O-1157 (R)	0.38	27.7	73
6-OH	7a, O-1591	55.1	3.320	60	14a, O-1299	3.02	166	55	17a, O-1926	6.09	1,450	238
7-OH	8a, O-1813	19.4	>6,000	>300	15a, O-1164	1.42	27.7	20	18a, O-1163	1.19	1,300	1,170
7-OH	(1R)-8a, O-1677	265	1,590	6	(1R)-15a, O-1675	2,690	139	0.05	(1R)-18a, O-1676	482	5,300	11
7-OH	(1S)-8a, O-1923	7.37	5,370	730	(1S)-15a, O-1945	0.3	15	50	(1S)-18a, O-1924	0.76	1,220	1,610
H	6b, O-1713	2.94	169	37	13b, O-1229 (R)	0.49	2.19	5	16b, O-1228	0.57	5,95	10
6-OH	7b, O-1627	246	260	1	14b, O-1814	7.7	34.2	4	17b, O-1748	32	180	6
7-OH	8b, O-1816	45	677	15	15b, O-1981	1.26	5.57	4	18b, O-1952	2.8	94	34
H	6c, O-1104	408	7,990	20	13c, O-381 (WIN)	11.0	160	15	16c, O-2024	17.9	1,130	63
6-OH	7c, O-1588	>29,000	>20,000	1	14c, O-1817	477	>20,000	>42	17c, O-1755	739	5,820	8
7-OH	8c, O-1927	7,730	>0,000	1	15c, O-1983	123	>10,000	>80	18c, O-1951	110	>20,000	>120
H	6d, O-1449	2,590	28,600	11	13d	65	N/A	-	16d	N/A	N/A	-
6-OH	7d, O-1644	>150,000	>100,000	1	14d, O-1816	6,150	88,000	14	17d, O-1589	3,550	>10,000	>3
7-OH	8d, O-1944	>10,000	>10,000	1	15d, O-1953	255	>10,000	>43	18d, O-1954	518	>100,000	>190

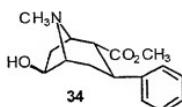
Table 3 presents binding data for the 7-keto, 6 α - and 7 α -hydroxy, and 3-diarylmethoxy compounds. Table 3 shows the inhibition of ^3H WIN 35,428 binding to the dopamine transporter and ^3H citalopram binding to the serotonin transporter in rhesus or cynomolgus monkey caudate-putamen. Studies were conducted in monkey striatum because this tissue (Meltzer, P. C. et al., *Med. Chem. Res.* 1998, 8, 12-34) is used in an ongoing investigation of structure activity relationships at the DAT, and meaningful comparisons with an extensive database can be made. Competition studies were conducted with a fixed concentration of radioligand and a range of concentrations of the test drug. All drugs inhibited ^3H WIN 35,428 and ^3H citalopram binding in a concentration-dependent manner. Each value is the mean of 2 or more independent experiments each conducted in different brains and triplicate. Errors generally do not exceed 15% between replicate experiments. Highest doses tested were generally 10-100 μM .

Table 3.

Compound	IC ₅₀ (nM)		IC ₅₀ (nM)				
	DAT	SERT	DAT	SERT			
19	O-2097	14.1	290	30b	O-2032	3.04	991
20	O-2096	14.2	7,038	32a	O-2070	448	4,850
23	O-2074	0.81	97	32b	O-2031	6,300	9,560
26	O-2099	1.1	2,520	33 ^a	O-2016	48	533
30a	O-2015	33.2	10,700	34 ^b	O-1754	32,600	>20,000



20 a.



b.

The bridge-hydroxylated compounds of the present invention provide a broad array of molecules including compounds that bind with very high affinity. Selectivity for inhibition of the DAT versus the serotonin transporter (SERT) is another property of tropanes of
5 considerable relevance for development of medications and for probes useful to image the DAT in living brain. Preferred compounds for DAT imaging agents have high DAT:SERT selectivity.

The compounds of the present invention can exhibit extremely potent and selective binding for the DAT. Preferred compounds of the
10 present invention exhibit the desired target:non-target (DAT:SET) specificity. Preferably, the selectivity ratio of binding of SERT to binding of DAT is greater than about 10, preferably greater than about 30 and more preferably 50 or more.

In addition, the compounds are potent, having an IC₅₀ less than about 500 nM, preferably less than 60 nM, more preferably less than about 20, and most preferably less than about 10.

Using the combination of selectivity (SERT/DAT ratio) and potency (IC₅₀) information for these compounds, one of ordinary skill in the art can readily select the appropriate compound for the desired application, 20 e.g., imaging or treatment.

For example, for cocaine medications high DAT:SERT selectivity may not be necessary. Even though the parent compound cocaine is relatively non-selective for all three monoamine transporters, and an abundance of evidence suggests that DAT blockade is a significant
25 contributor to the reinforcing effects of cocaine, self-administration is sustained in DAT knockout mice (Rocha, B. A. et al., *Nat. Neurosci.* 1998, 1 (2), 132-137). One possible interpretation of these findings is that cocaine blocks transport of dopamine via other transporters in brain regions critical to maintaining self-administration (Sora, I. et al., *Proc. Natl. Acad. Sci. USA* 1998, 95, 7699-7704). Thus, compounds both selective and non-selective for the DAT should be assessed in screening programs for cocaine medications. The methods of the present invention

enable the design of bridge-substituted tropanes with either a high or low degree of DAT:SERT selectivity.

Introduction of functionality at the 6,7-bridge of 3-phenyltropanes has been studied (Chen, Z. et al., *J. Med. Chem.* 1996, 39, 4744-4749;

- 5 Lomenzo, S. A. et al., *J. Med. Chem.* 1997, 40, 4406-4414; Simoni, D. et al., *J. Med. Chem.* 1993, 36, 3975-3977; Chen, Z.; Meltzer, P. C., *Tetrahedron Lett.* 1997, 38, 1121-1124; Lomenzo, S. A. et al., *Med. Chem. Res.* 1998, 8, 35-42). In general, steric bulk at either position has reduced the affinity of these compounds for the dopamine transporter.

- 10 Simple introduction of an hydroxyl group on a 3-aryl tropane is also not sufficient to provide potent DAT inhibitors (Zhao, L.; Kozikowski, A. P., *Tet. Lett.* 1999, 40, 7439). Based upon the SAR that we have uncovered in other bicyclo[3.2.1]octane series (Meltzer, P. C. et al., *J. Med. Chem.* 1997, 40, 2661-2673; Meltzer, P. C. et al., *Med. Chem. Res.* 1998, 8, 12-

- 15 34), in order to achieve high potency and selectivity, the methods of the present invention use derivatives of the 3,4-dichlorophenyl substituted template as the starting point, since this substitution, and to a similar extent the 2-naphthyl substitution (Davies, H. M. L. et al., *J. Med. Chem.* 1994, 37, 1262-1268), have provided among the most potent DAT

- 20 inhibitors. Furthermore, SAR studies have demonstrated that selectivity of binding to the DAT versus binding to the SERT can be obtained in the 3 α -aryl as well as the 2,3-unsaturated series of compounds (Meltzer, P. C. et al., *Med. Chem. Res.* 1998, 8, 12-34).

Table 2 presents the 6- and 7-hydroxylated compounds as well as the bridge unsubstituted ($R_2 = H$) parent compounds for comparison. In general, the 7-hydroxy compounds (**8**, **15**, **18**) are more potent than the 6-hydroxy compounds (**7**, **14**, **17**). Comparison of the 2,3-unsaturated racemates, **6a** with **7a** and **8a** show that the unsubstituted compound **6a** is significantly more potent than either **7a** or **8a**. When only active enantiomers are compared, it is apparent that the hydroxylated analogs are of comparable potencies to the bridge unsubstituted compounds. Compound (**1R**)-**13a** exhibits DAT IC₅₀ = 1.09 nM while the active (**1S**)-

15a is about three times more potent (0.3 nM) and 25-fold more selective than **13a** (Table 3).

When the aromatic ring is oriented in the 3 α -configuration, the parent-unsubstituted compound (**1R**)-**16a** has DAT IC₅₀ = 0.38 nM and the hydroxylated enantiopure compound (**1S**)-**18a** shows a similar value of 0.76 nM. In this case, the hydroxylated compound shows a selectivity ratio of 1610 and is therefore 22-fold more selective than **16a**. However, (**1S**)-**18a** is 32-fold more selective than (**1S**)-**15a** thus demonstrating the enhanced selectivity of 3 α -configured compounds over their 3 β -counterparts. Thus, introduction of an hydroxyl at C7 has, at least, maintained potency of DAT inhibition and retained or may have increased selectivity versus inhibition of the SERT.

This increase in selectivity is evident in the 6-hydroxy compounds **14a** and **17a** as well. The fact that the *1R* configured compounds (**1R**)-**8a**, (**1R**)-**15a** and (**1R**)-**18a** are considerably less potent than the *1S* enantiomers points, once again, to the biological enantioselectivity of the DAT and SERT.

The results show three properties of the compounds of the present invention. First, the bridge hydroxylated compounds confirm biological enantioselectivity. Second, the 7-hydroxylated compounds are more potent at the DAT than their 6-hydroxyl counterparts. Third, the bridge hydroxylated compounds are more selective DAT inhibitors than the unsubstituted analogs.

The effects of substitution on the C3-aryl ring of the bridge hydroxylated compounds in Table 2 mimic other tropane series (Meltzer, P. C. et al., *Med. Chem. Res.* 1998, *8*, 12-34; Meltzer, P. C. et al., *J. Med. Chem.* 1993, *36*, 855-862) including the 8-oxa (Meltzer, P. C. et al., *J. Med. Chem.* 1997, *40*, 2661-2673) and 8-carba (Meltzer, P. C. et al., *J. Med. Chem.* 2000, *43*, 2982-2991) compounds. Thus, for substituents on the C3-position, 3,4-dichlorophenyl compounds are more potent inhibitors of the DAT than the 3-(2-naphthyl) compounds, which are more potent than the 3-fluorophenyl, which in turn are more potent than phenyl compounds.

Further, selectivity for inhibition of the DAT versus the SERT is greater for the compounds of the present invention bearing a 3α -aryl substituent as compared with a 3β -aryl substituent. Thus, certain preferred compounds have a 3α -aryl substituent, i.e., they are in the boat conformation.

The 2,3-unsaturated analogs generally display the same rank order of potency at the DAT. They manifest good selectivity, particularly for those compounds that are potent inhibitors. Thus for both 6- and 7-hydroxylated compounds, 3,4-dichloro substitution provides similar or slightly higher potency at the DAT than for introduction of a C3-(2-naphthyl) group. Both are significantly superior to a 4-fluoro group which, in turn, is more potent than the unsubstituted phenyl ring compound. In the 7-hydroxy series, the racemic 3β -configured 3,4-dichloro compound **15a** manifests a DAT IC₅₀ of 1.42 nM compared with 1.26 nM for the 2-naphthyl **15b**, 123 nM for the 4-fluoro **15c**, and 235 nM for the unsubstituted **15d**. A similar relationship is seen in the 3α -configured series: **18a** (3,4-dichloro) > **18b** (2-naphthyl) > **18c** (4-fluoro) > **18d** (H) and the 2,3-enes: **8a** (3,4-dichloro) > **8b** (2-naphthyl) > **8c** (4-fluoro) > **8d** (H). Interestingly, either 6- or 7-hydroxy substituents reduce affinity of 4-fluoro substitution.

Selectivity for inhibition of the DAT versus the SERT is likewise similar to that evidenced in all other series (Meltzer, P. C. et al., *J. Med. Chem.* 1997, 40, 2661-2673; Meltzer, P. C. et al., *J. Med. Chem.* 2000, 43, 2982-2991; Meltzer, P. C. et al., *Med. Chem. Res.* 1998, 8, 12-34).

The parent compounds in which no bridge hydroxylation is present (**6**, **13**, **16**) model the series (Table 2): 2,3-ene (**6a**) > 3α (**16a**) > 3β (**13a**). Thus, the 3β configured compounds are generally least selective and the 2,3-ene and 3α -compounds are more selective. This difference in selectivity diminishes where compounds are intrinsically less potent DAT inhibitors. An example of this is evident in the comparison between the potent 3,4-dichloro series and the weak ring-unsubstituted compounds. Thus **8a**, **15a**, and **18a** have selectivities of SERT/DAT ranging from 20 to 1,170 while the unsubstituted **8d**, **15d**, and **18d** have selectivities that

range from 1-190. While the inventors do not wish to be bound by theory, it may be concluded that a tight fit between the ligand and the relevant transporter enhances selectivity.

As noted in earlier work (Meltzer, P. C. et al., *Med. Chem. Res.*

- 5 1998, 8, 12-34), the SERT appears to be more discriminating since DAT inhibition is often similar across the C3-altered compounds in contrast to SERT inhibition which differs markedly across the series. Similarly **20** and **26** (3 α) are more selective than **19** and **23** (3 β) (Table 3).

From these data it may be concluded that: First, the general SAR
10 of the tropanes is maintained in that the rank order of substitution at the C3 position remains 3,4-dichlorophenyl > 2-naphthyl > 4-fluorophenyl > phenyl. Second, the general SAR of the bicyclo[3.2.1]octane series is maintained in that the 3 α -aryl compounds are more selective than the 3 β -aryl compounds.

15 The DAT is enantioselective (Reith, M. E. A. et al., *Biochem. Pharmacol.* 1986, 35, 1123-1129; Ritz, M. C. et al., *Science* 1987, 237, 1219-1223; Madras, B. K. et al., *J. Pharmacol. Exp. Ther.* 1989, 251, 131-141; Meltzer, P. C. et al., *J. Med. Chem.* 1994, 37, 2001-2010; Sershen, H. et al., *Neuropharmacology* 1980, 19, 1145-1148; Carroll, F. I. et al., *J. Med. Chem.* 1992, 35, 969-981; Carroll, F. I. et al., in *Drug Design for Neuroscience*; A. P. Kozikowski, Ed.; Raven Press, Ltd. New York, 1993; 149-166). Accordingly, the biological enantioselectivity of the most active parent bridge hydroxylated compounds, namely **8a**, **15a**, and **18a** was studied. Table 2 shows that the 1S enantiomers are significantly more potent inhibitors than their 1R counterparts. Thus, (1S)-**8a**, (1S)-**15a**, and (1S)-**18a** all manifest DAT IC₅₀s of 0.3-7.4 nM while the 1R enantiomers (1R)-**8a**, (1R)-**15a**, and (1R)-**18a** manifest DAT IC₅₀'s in the range of 265 - 2,690 nM. Selectivities for DAT versus SERT inhibition follow similarly. Thus the less active 1R-enantiomer series of the 3,4-dichlorophenyl analog manifests selectivities that range from 0.05 - 11-fold ((1R)-**8a**, (1R)-**15a** and (1R)-**18a**). In contrast, the active 1S-enantiomers show clear differences in selectivity (50 - 1,610 for (1S)-**15a**,

(**1S**)-**8a** and (**1S**)-**18a**). Biological enantioselectivity is conserved for bridge hydroxylated tropanes.

Although the 7 β -hydroxy-C2 α -methylester **33** is less potent (Table 3) at both the DAT (IC_{50} = 48 nM) and the SERT (IC_{50} = 533 nM) than the C2 β analog **15a** (DAT: 1.42 nM; SERT: 27.7 nM), it is still almost twice as potent as cocaine at the DAT. In the absence of ring substitution, as in **34**, the 6-hydroxy-C2 α -compound is inactive.

Replacement of the C2 ester with a C2 ethyl ketone leads to quite potent inhibitors (Table 3). Thus, **23** manifests a DAT IC_{50} = 0.81 nM and a SERT IC_{50} = 97 nM. As may be anticipated, when a C2 ethyl ketone is present in a 3 α -3,4-dichlorophenyl analog, as in **26**, one of the most selective and potent DAT inhibitors is discovered (DAT: 1.1 nM; SERT: 2,520 nM) (see Scheme 3).

The orientation of the oxygen at the 6 or 7- position is not absolutely crucial for biological activity since both α -, β - and even "planar" 7-ketones manifest nanomolar binding affinity at the DAT. Indeed, if this is so, then the hydrogen bonding between an hydroxyl at this position and the nitrogen may be of limited consequence. In this regard, the 7 α -OH compound **30b** (Scheme 5) is about half as potent (IC_{50} = 3.04 nM) as the 7 β -OH analog **18a** at the DAT (IC_{50} = 1.19 nM). The 7-keto analog **19** (Scheme 2) remains quite potent at 14.1 nM. In the 6-OH series, the same holds true; the 6 β **17a** binds with an affinity of 6.09 nM, and the 6 α **30a** manifests an IC_{50} = 33.2 nM.

Three conclusions emerge: First, 2 β -substitution provides greater potency than 2 α -substitution. Second, replacement of the C2-ester with a C2-ketone retains potency at the DAT. Third, both 6 α - and 7 α -hydroxylated and 7-keto compounds prove potent DAT inhibitors.

The compounds of the invention can be prepared either as free bases or as a pharmacologically active salt thereof such as hydrochloride, tartrate, sulfate, naphthalene-1,5-disulfonate or the like.

The present invention also provides pharmaceutical compositions, preferably comprising the compounds of the present invention in a pharmaceutically acceptable carrier. Pharmaceutically acceptable

carriers are well known to those skilled in the art. An exemplary pharmaceutical composition is a therapeutically effective amount of a compound of the invention optionally included in a pharmaceutically-acceptable and compatible carrier. The term "pharmaceutically-
5 acceptable and compatible carrier" as used herein, and described more fully below, refers to e.g., one or more compatible solid or liquid filler diluents or encapsulating substances that are suitable for administration to a human or other animal. The route of administration can be varied but is principally selected from intravenous, nasal and oral routes. For
10 parenteral administration, e.g., it will typically be injected in a sterile aqueous or non-aqueous solution, suspension or emulsion in association with a pharmaceutically-acceptable parenteral carrier such as physiological saline.

The term "therapeutically-effective amount" is that amount of the present pharmaceutical compositions which produces a desired result or exerts a desired influence on the particular condition being treated. Various concentrations may be used in preparing compositions incorporating the same ingredient to provide for variations in the age of the patient to be treated, the severity of the condition, the duration of the treatment and the mode of administration. An effective dose of the compound is administered to a patient based on IC₅₀ values determined in vitro.

The term "compatible", as used herein, means that the components of the pharmaceutical compositions are capable of being commingled with the compounds of the present invention, and with each other, in a manner such that there is no interaction that would substantially impair the desired pharmaceutical efficacy.

Dose of the pharmaceutical compositions of the invention will vary depending on the subject and upon particular route of administration used. Pharmaceutical compositions of the present invention can also be administered to a subject according to a variety well-characterized protocols.

In a preferred embodiment, the pharmaceutical composition is a liquid composition in pyrogen-free, sterilized container or vial. The container can be unit dose or multidose.

The compounds and pharmaceutical preparations of the present

- 5 invention can be used to inhibit the %-hydroxytryptamine reuptake of a monoamine transporter, particularly reuptake by the dopamine transporter, serotonin transporter or norepinephrine transporter.

Dysfunction of dopamine neurons has been implicated in several neuropsychiatric diseases. Imaging of the dopamine neurons offers

- 10 important clinical information relevant to diagnosis and therapeutic treatments. Dopamine neurons produce dopamine, release the neurotransmitter and remove the released dopamine with a dopamine transporter protein. Compounds that bind to the dopamine transporter are effective measures of dopamine neurons and can be transformed into imaging agents for PET and for SPECT imaging. In identifying a suitable compound for the dopamine transporter, an essential first step is to measure the affinity and selectivity of a candidate at the dopamine transporter. The affinity is measured by conducting radioreceptor assays. A radiolabeled marker for the transporter, e.g., (³H)WIN 35,428,
- 15 20 is incubated with the unlabeled candidate and a source of the transporter, usually brain striatum. The effect of various concentrations of the candidate on inhibiting (³H)WIN 35,428 binding is quantified. The concentration of the compound that inhibits 50% of (³H)WIN 35,428 bound to the transporter (IC₅₀ value) is used as a measure of its affinity
- 25 for the transporter. A suitable range of concentrations of the candidate typically is 1 – 10 nM.

- It is also important to measure the selectivity of the candidate of the dopamine compared with the serotonin transporter. The serotonin transporter is also detectable in the striatum, the brain region with the highest density of dopamine neurons and in brain regions surrounding the striatum. It is necessary to determine whether the candidate compound is more potent at the dopamine than the serotonin transporter. If more selective (>10-fold), the probe will permit accurate

measures of the dopamine transporter in this region of interest or will provide effective treatment modality for the dopamine transporter.

Therefore, a measure of probe affinity of the serotonin transport is conducted by assays paralleling the dopamine transporter assays.

- 5 (3H)Citalopram is used to radiolabel binding sites on the serotonin transporter and competition studies are conducted with the candidate compound at various concentrations in order to generate an IC₅₀ value.

This invention will be illustrated further by the following examples. These examples are not intended to limit the scope of the 10 claimed invention in any manner. The Examples provide suitable methods for preparing compounds of the present invention. However, those skilled in the art may make compounds of the present invention by any other suitable means. As is well known to those skilled in the art, other substituents can be provided for the illustrated compounds by 15 suitable modification of the reactants.

All exemplified target compounds are fully analyzed (mp, TLC, CHN, GC and/or HPLC) and characterized (¹H NMR, ¹³C NMR, MS, IR) prior to submission for biological evaluation. The affinity of all the compounds for the DAT, SERT and NET are measured. NMR spectra are recorded on a 20 Bruker 100, a Varian XL 400, or a Bruker 300 NMR spectrometer.

Tetramethylsilane ("TMS") is used as internal standard. Melting points are uncorrected and are measured on a Gallenkamp melting point apparatus. Thin layer chromatography (TLC) is carried out on Baker Si 250F plates. Visualization is accomplished with iodine vapor, UV exposure or treatment 25 with phosphomolybdic acid (PMA). Preparative TLC is carried out on Analtech uniplates Silica Gel GF 2000 microns. Flash chromatography is carried out on Baker Silica Gel 40mM. Elemental Analyses are performed by Atlantic Microlab, Atlanta, GA and are within 0.4% of calculated values for each element. A Beckman 1801 Scintillation Counter is used for 30 scintillation spectrometry. 0.1% Bovine Serum Albumin ("BSA") and (-)-cocaine is purchased from Sigma Chemicals. All reactions are conducted under an inert (N₂) atmosphere.

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³H-WIN 35,428 (³H-CFT, 2 β -carbomethoxy-3 β -(4-fluorophenyl)-N-³H-methyltropane, 79.4-87.0 Ci/mmol) and ³H-citalopram (86.8 Ci/mmol) is purchased from DuPont-New England Nuclear (Boston, MA). (R)-(-)-Cocaine hydrochloride for the pharmacological studies was donated by the National Institute on Drug Abuse (NIDA). Fluoxetine was donated by E. Lilly & Co. HPLC analyses are carried out on a Waters 510 system with detection at 254 nm on a Chiralcel OC column (flow rate: 1 mL/min).

EXAMPLES

- 10 NMR spectra were recorded in CDCl₃, unless otherwise mentioned, on a JEOL 300 NMR spectrometer operating at 300.53 MHz for ¹H, and 75.58 MHz for ¹³C. TMS was used as internal standard. Melting points are uncorrected and were measured on a Gallenkamp melting point apparatus. Thin layer chromatography (TLC) was carried out on Baker Si250F plates. Visualization was accomplished with either UV exposure or treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on Baker Silica Gel 40 μ M. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA. HRMS was performed at Harvard University, MA. Optical rotations were measured on a Perkin Elmer 241 Polarimeter. All reactions were conducted under an inert (N₂) atmosphere. ³H-WIN 35,428 (2 β -carbomethoxy-3 β -(4-fluorophenyl)-N-³H)methyltropane, 79.4-87.0 Ci/mmol) and ³H)citalopram (86.8 Ci/mmol) were purchased from DuPont-New England Nuclear (Boston, MA). (1S)-(-)-Camphanic chloride (98% ee) was purchased from Aldrich. A Beckman 1801 scintillation counter was used for scintillation spectrometry. Bovine serum albumin (0.1%) was purchased from Sigma Chemicals. (R)-(-)-Cocaine hydrochloride for the pharmacological studies was donated by the National Institute on Drug Abuse (NIDA). Room temperature is ca. 22 °C. TMSBr: trimethylsilyl bromide. Solution A: 2-hydroxy-2-methylpropanol/1,2-dichloroethane, 37:63. Yields have not been optimized.

EXAMPLE 1:6-Hydroxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo[3.2.1]octane (1a) and 7-hydroxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo[3.2.1]octane (1b).

Acetonedicarboxylic acid (40 g, 0.27 mol) was added slowly to a
5 solution of acetic acid (60 mL) and acetic anhydride (43 mL) at 0 °C. The mixture was stirred below 10 °C. The acid dissolved slowly and a pale yellow precipitate was formed over 3 h. The product was filtered, washed with glacial acetic acid (30 mL), followed by benzene (100 mL). The resultant white powder was dried at high vacuum to afford 30 g of the
10 desired acetonedicarboxylic acid anhydride (86%): mp 137-138 °C (lit.³⁸ 137.5-138.5 °C). Cold dry methanol (160 mL) was added to acetonedicarboxylic acid anhydride (50 g, 0.39 mol). The solution was allowed to stand for 1 h and filtered. The filtrate, acetonedicarboxylic acid monomethylester,³⁸ was used directly in the following reaction. A
15 mixture of 2,5-dimethoxydihydrofuran (53.6 g, 0.41 mol) and 3 M aqueous HCl (1 L) was allowed to stand for 12 h at 22 °C. The brown solution was cooled to 0 °C and ice (500 g) added before being neutralized with aqueous 3 M NaOH (1 L). Methylamine hydrochloride (41 g, 0.62 mol) in H₂O (300 mL) was added to this solution followed by
20 the preformed methanol solution (160 mL above) of acetonedicarboxylic acid monomethylester and sodium acetate (50 g) in H₂O (200 mL). The mixture (pH 4.5) was stirred for 2 days at 22 °C. The resultant red solution was extracted with hexanes (500 mL x 2) to remove non-polar by-products. The aqueous solution was neutralized and saturated by
25 adding solid K₂CO₃ (960 g). The saturated solution was extracted with CH₂Cl₂ (300 mL x 3) and the combined extracts were dried over anhydrous K₂CO₃, filtered and concentrated to provide the crude product (21.6 g). The aqueous solution was extracted with Solvent A and the combined extracts were dried over anhydrous K₂CO₃, filtered and
30 concentrated to provide a pale yellow solid that was found to be a mixture of 6- and 7-hydroxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo[3.2.1]octanes of good purity (30.6 g) and were used without further purification. The crude product obtained from the CH₂Cl₂

extracts was purified by column chromatography {10% NEt₃, 60% EtOAc in hexanes (30-90%), followed by 10% NEt₃, 5% MeOH and 85% EtOAc} to afford 6.2 g of a mixture of 6 β - and 7 β -methoxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo{3.2.1}octane (Chen, Z.; Meltzer, P. C., 5 *Tetrahedron Lett.* 1997, 38, 1121-1124) as an oil: *R*_f 0.44 (10% NEt₃, 20% EtOAc in hexanes) and 12.8 g of 6 β - and 7 β -hydroxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo{3.2.1}octane as yellow solids (**1a** and **1b**). The total yield of 6 β - and 7 β -hydroxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo{3.2.1}octane was 43.4 g (52%). ¹H NMR of **1a** (mixture 10 of the keto-2 α - and keto-2 β -epimers and the intermediate enol compounds) δ 4.18-4.02 (m, 1H), 3.89-3.85 (m, 1H), 3.78, 3.76 (2s, 3H), 3.45-3.36 (m, 1H), 3.21 (d, *J* = 6 Hz, 1H), 2.75-2.62 (m, 2H), 2.40, 2.38 (2s, 3H), 2.37-2.22 (m, 1H), 2.1-1.92 (m, 2H). ¹H NMR of **1b** (observed in the intermediate enol form only) δ 11.83 (s, 1H), 4.06 (dd, *J* = 5.8, 2.0 15 Hz, 1H), 3.78 (s, 3H), 3.66 (s, 1H), 3.37 (t, *J* = 4.7 Hz, 1H), 2.66 (dd, *J* = 18.9, 4.6 Hz, 1H), 2.39 (s, 3H), 2.02-1.96 (m, 1H), 1.73 (d, *J* = 18.6 Hz, 1H).

EXAMPLE 2: 6 β -Methoxymethoxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo{3.2.1}octane (**2a**) and 7 β -Methoxymethoxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo{3.2.1}octane (**2b**).

To a solution of a mixture of 6 β - and 7 β -methoxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo{3.2.1}octane (**1a** and **1b**) 25 (30.6 g, 140 mmol) in anhydrous CH₂Cl₂ (600 mL) and dimethoxymethane (170 mL), *p*-toluenesulfonic acid monohydrate (31 g, 160 mmol) was added in a 2 L flask fitted with a Soxhlet extractor containing 4 Å molecular sieves. The reaction mixture was heated to reflux until complete. The mixture was cooled and treated with saturated aqueous Na₂CO₃ (200 mL) and extracted with CH₂Cl₂ (300 mL x 4). The combined organic extracts were dried over K₂CO₃, filtered and 30 concentrated to obtain a mixture of MOM protected alcohols. The

mixture was separated by column chromatography ({5-10% NEt₃, 65% EtOAc in hexanes (30-50%)} to obtain 6 β -hydroxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo{3.2.1}octane **2a** (11.0 g, 30%) and 7 β -hydroxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo{3.2.1}octane **2b** (10.6 g, 28%) along with a mixture of the MOM protected alcohols **2a** and **2b** (2.9 g, 8%).

2a: yellow oil: *R*_f 0.55 (10% Et₃N in EtOAc); ¹H NMR (mixture of the keto-2 α - and keto-2 β -epimers and the intermediate enol compounds) δ 11.69 (s, enol H), 4.63, 4.62, 4.60 (3s, 2H), 4.10-3.96 (m, 2H), 3.88 (d, J = 6.6 Hz, 1H), 3.76, 3.75, 3.74 (3s, 3H), 3.36, 3.34 (2s, 3H), 3.11-2.71 (m, 1H), 2.69, 2.62, 2.41 (3s, 3H) 2.34-1.91 (m, 2H). **2b:** yellow solid: *R*_f 0.38 (10% Et₃N, 30% EtOAc and 60% hexanes); ¹H NMR (observed in the intermediate enol form only) δ 11.77 (s, 1H), 4.69 (d, J = 6.6 Hz, 1H), 4.63 (d, J = 6.6 Hz, 1H), 4.06 (dd, J = 1.6, 7.2 Hz, 1H), 3.81 (s, 1H), 3.79 (s, 3H), 3.45 (dd, J = 4.6, 6.6 Hz, 1H), 3.36 (s, 3H), 2.75-2.66 (m, 1H), 2.43 (s, 3H), 2.18 (dd, J = 7.4, 14.3 Hz, 1H), 1.99 (dd, J = 7.4, 14.3 Hz, 1H), 1.79 (d, J = 18.7 Hz, 1H).

EXAMPLE 3:2-Carbomethoxy-3-trifluoromethylsulfonyloxy-7 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}oct-2-ene (3b).

To a solution of 2-carbomethoxy-7 β -methoxymethoxy-8-methyl-3-oxo-8-azabicyclo{3.2.1}octane, **2b** (4.25 g, 16.5 mmol) in THF (150 mL), sodium bistrimethylsilylamide (25 mL; 1.0 M solution in THF) was added dropwise at -70 °C under nitrogen. After stirring for 30 min, *N*-phenyltrifluoromethanesulfonimide (7.06 g, 19.8 mmol) was added in one portion at -70 °C. The reaction was allowed to warm up to 22 °C and stirred overnight. The volatile solvents were removed on a rotary evaporator. The residue was dissolved in CH₂Cl₂ (200 mL), washed with H₂O (100 mL) and brine (100 mL). The dried (MgSO₄) CH₂Cl₂ layer was concentrated to dryness and purified by flash chromatography (2-10% Et₃N, 15-30% EtOAc in hexanes) to afford 3.63 g (57%) of **3b** as a pale

yellow oil: R_f 0.29 (10% Et₃N, 30% EtOAc, 60% hexanes); ¹H NMR of **3b** δ 4.74 (d, J = 6.8 Hz, 1H), 4.65 (d, J = 6.8 Hz, 1H), 4.21 (dd, J = 1.6, 7.3 Hz, 1H), 4.0 (s, 1H), 3.83 (s, 3H), 3.56-3.50 (m, 1H), 3.37 (s, 3H), 2.80 (dd, J = 4.1, 18.4 Hz, 1H), 2.44 (s, 3H), 2.21 (dd, J = 7.4, 14.0 Hz, 1H), 5 2.02 (dd, J = 7.4, 14.1 Hz, 1H), 1.89 (d, J = 18.7 Hz, 1H); HRMS Cal (M+1): 390.0856; Found 390.0811.

EXAMPLE 4:2-Carbomethoxy-3-(trifluoromethyl)sulfonyloxy-6β-methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}oct-2-ene (3a**).**

10 Prepared as described above for **3b** (64%): R_f 0.45 (10% Et₃N, 30% EtOAc, 60% hexanes); ¹H NMR (100 MHz): δ 4.64 (s, 2H), 4.07 (dd, 1H), 3.81 (s, 3H), 3.5-3.30 (m, 2H), 3.36 (s, 3H), 2.85 (dd, 1H), 2.44 (s, 3H), 2.4-1.8 (m, 3H).

15 **EXAMPLE 5:General procedures for Suzuki coupling reactions to obtain **4** and **5**.**

To a solution of 2β-carbomethoxy-3-((trifluoromethyl)sulfonyl)oxy-7β- (or 6β-) methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}oct-2-ene, **3** (1 eq) in diethoxymethane was added LiCl (2 eq), Na₂CO₃ (2 M aqueous 20 solution, 2 eq) and the aryl boronic acid (1.1 eq). The solution was stirred and deoxygenated by bubbling N₂ into the solution for 15 min before the addition, in one portion, of tris(dibenzylideneacetone)dipalladium(0) (0.1 eq) under a strong stream of N₂. After being further deoxygenated for another 0.5 h, the solution was heated to reflux under N₂ until no 25 starting material remained (~ 3-6 h) (TLC). The mixture was cooled to 22 °C and filtered through Celite. The Celite was washed with EtOAc. The combined organic layers were separated and the aqueous layer was extracted with EtOAc. The organic layer was combined and dried over K₂CO₃. The solvent was removed and the residue was purified by flash 30 column chromatography (10% Et₃N, 30% EtOAc, 60% hexanes) to afford the coupled compounds.

EXAMPLE 6:2-Carbomethoxy-3-(3,4-dichlorophenyl)-6-

The general procedure described above was followed. The product was obtained as an oil (86%): R_f 0.16 (10% Et₃N, 20% EtOAc, 70%

- 5 hexanes; ^1H NMR δ 7.39 (d, 1H), 7.21 (d, 1H), 6.95 (dd, 1H), 4.66 (s, 2H),
 4.11 (dd, 1H), 3.95 (d, 1H), 3.35 (s, 3H), 3.39-3.35 (m, 4H), 2.70 (dd, 1H),
 2.54-2.43 (m, 4H), 2.19 (ddd, 1H), 2.02 (d, 1H).

EXAMPLE 7:2-Carbomethoxy-3-(2-naphthyl)-6 β -methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (4b).

The general procedure described above was followed. The product was obtained as an oil (53%): R_f 0.36 (10% Et₃N, 30% EtOAc, 60%

- hexane); ^1H NMR δ 7.84–7.77 (m, 3H), 7.59 (s, 1H), 7.50–7.44 (m, 2H),
 7.24 (dd, 1H), 4.69 (s, 2H), 4.20 (dd, 1H), 4.00 (d, 1H), 3.43 (s, 3H), 3.41–
 15 3.38 (m, 4H), 2.82 (dd, 1H), 2.59–2.50 (m, 4H), 2.26–2.17 (m, 2H).

EXAMPLE 8-2: Carbomethoxy-3-(4-fluorophenyl)-6 β -methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (4c).

The general procedure described above was followed. The product was obtained as a yellow oil (93%): R_f 0.12 (10% Et₃N, 20% EtOAc, 70% hexane); ¹H NMR δ 7.11-6.97 (m, 4H), 4.67 (s, 2H), 4.12 (dd, 1H), 3.94 (d, 1H), 3.49 (s, 3H), 3.38-3.33 (m, 4H), 2.71 (dd, 1H), 2.50-2.44 (m, 4H), 2.19 (ddd, 1H), 2.06 (d, 1H).

- 25 EXAMPLE 9:2-Carbomethoxy-3-phenyl-6 β -methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (4d).

The general procedure described above was followed. The product was obtained as a light yellow oil (89%): R_f 0.16 (10% Et₃N, 20% EtOAc, 70% hexane); ¹H NMR δ 7.36-7.23 (m, 3H), 7.14-7.11 (m, 2H), 4.67 (s, 3H), 4.16 (dd, 1H), 4.03 (d, 1H), 3.47 (s, 3H), 3.43 (m, 1H), 3.38 (s, 1H), 2.87 (dd, 1H), 2.58-2.51 (m, 4H), 2.23 (ddd, 1H), 2.15 (d, 1H).

EXAMPLE 10: 2-Carbomethoxy-3-(3,4-dichlorophenyl)-7 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}oct-2-ene (5a).

The general procedure described above was followed. The product
5 was obtained as an oil (80%): R_f 0.33 (10% Et₃N, 20% EtOAc, 70%
hexane); ¹H NMR (100 MHz) δ 7.40 (d, 1H), 7.19 (d, 1H), 6.93 (dd, 1H),
4.71 (m, 2H), 4.24 (dd, 1H), 3.91 (s, 1H), 3.56 (s, 3H), 3.48 (bs, 1H), 3.39
(s, 3H), 2.52 (s, 3H), 2.90-1.5 (m, 4H); ¹³C NMR δ 168.3, 144.8, 142.0,
133.4, 132.8, 131.3, 129.9, 128.2, 127.4, 96.4, 83.2, 66.3, 57.5, 56.5,
10 52.7, 41.5, 36.0, 35.7.

EXAMPLE 11: 2-Carbomethoxy-3-(2-naphthyl)-7 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}oct-2-ene (5b).

The general procedure described above was followed. The product
15 was obtained as a yellow oil (100%): R_f 0.52 (10% Et₃N, 20% EtOAc, 70%
hexane); ¹H NMR δ 7.79 (m, 3H), 7.57 (s, 1H), 7.48 (m, 2H), 7.22 (d, 1H),
4.74 (dd, 2H), 4.35 (dd, 1H), 3.95 (s, 1H), 3.52-3.46 (m, 4H), 3.41 (s, 3H),
2.85 (dd, 1H), 2.58 (s, 3H), 2.27 (dd, 1H), 2.15 (dd, 1H), 1.98 (d, 1H).

EXAMPLE 12: 2-Carbomethoxy-3-(4-fluorophenyl)-7 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}oct-2-ene (5c).

The general procedure described above was followed. The product
was obtained as an oil (100%): R_f 0.53 (10% Et₃N, 20% EtOAc, 70%
hexane); ¹H NMR δ 7.15-7.00 (m, 4H), 4.75 (dd, 2H), 4.29 (dd, 1H), 3.89
25 (s, 1H), 3.53 (s, 3H), 3.45 (m, 1H), 3.39 (s, 3H), 2.73 (dd, 1H), 2.51 (s,
3H), 2.25 (dd, 1H), 2.07 (dd, 1H), 1.85 (d, 1H).

EXAMPLE 13: 2-Carbomethoxy-3-phenyl-7 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}oct-2-ene (5d).

The general procedure described above was followed. The product
was obtained as an oil (29%): R_f 0.56 (10% Et₃N, 30% EtOAc, 70%
hexane); ¹H NMR δ 7.32-7.27 (m, 3H), 7.12-7.07 (m, 2H), 4.73 (dd, 2H),

4.30 (dd, 1H), 3.89 (s, 1H), 3.50 (s, 3H), 2.47 (m, 1H), 3.38 (s, 3H), 2.76 (dd, 1H), 2.52 (s, 3H), 2.25 (dd, 1H), 2.09 (dd, 1H), 1.88 (d, 1H).

EXAMPLE 14: General procedure for SmI₂ reduction reactions

5 **to obtain 9-12.**

Note that the 3 α and 3 β isomers are obtained and are separated by column chromatography. To a THF (anhydrous, 5-10 mL) solution of 2-carbomethoxy-3-aryl-7- (or 6-) methoxymethoxy-8-azabicyclo[3.2.1]oct-2-ene and anhydrous methanol (20 eq) at -78 °C under N₂ was added

- 10 SmI₂ (0.1 M solution in THF, 8 eq) dropwise. The resulting solution was kept stirring at -78 °C for 4 h and was then quenched with H₂O (10 mL). After warming to 22 °C, sat. NaHCO₃ was added and the precipitate was filtered through a Celite pad. The pad was washed with EtOAc and the aqueous layer was back extracted with EtOAc three times. The organic layers were combined, washed with brine and dried over K₂CO₃. The solvent was removed and the residue was purified by two consecutive flash columns (First: 10% Et₃N, 30% EtOAc, 60%, hexanes; Second: 5% MeOH, 95% CHCl₃) to obtain the 2 β , 3 β - (**9** and **11**) and 2 β , 3 α - (**10** and **12**) isomers.

20 **EXAMPLE 15: 2 β -Carbomethoxy-3 β -(3,4-dichlorophenyl)-6 β -methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (**9a**) and 2 β -carbomethoxy-3 α -(3,4-dichlorophenyl)-6 β -methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (**10a**).**

- 25 The title compounds were prepared as in the general procedure given above. Compound **9a** (an oil: 16%) could not be readily purified and was therefore carried through to the next step as is (see **14a**). *R*_f 0.67 (Et₃N 10%, EtOAc 30%, hexanes 60%). Compound **10a** was obtained as an oil (8%): *R*_f 0.30 (3% MeOH, CHCl₃); *R*_f 0.69 (Et₃N 10%, EtOAc 30%, hexanes 60%). ¹H NMR δ 7.32 (d, 1H), 7.25 (d, 1H), 7.01 (d, 1H), 4.64 (dd, 2H), 4.12 (dd, 1H), 3.59-3.55 (m, 5H), 3.39-3.01 (m, 5H), 2.55 (s, 3H), 2.46-2.25 (m, 3H), 2.10 (dd, 1H), 1.29 (ddd, 1H).

EXAMPLE 16: 2 β -Carbomethoxy-3 β -(2-naphthyl)-6 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}octane (**9b**) and 2 β -carbomethoxy-3 α -(2-naphthyl)-6 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}octane (**10b**).

The title compounds were prepared as in the general procedure given above. Compound **9b** was obtained as an oil (38%): R_f 0.30 (3% MeOH/CHCl₃); ¹H NMR δ 7.75 (t, 3H), 7.65 (s, 1H), 7.46-7.33 (m, 3H), 4.67 (s, 2H), 4.32 (dd, 1H), 3.80 (d, 1H), 3.47 (s, 1H), 3.44 (s, 3H), 3.39 (s, 3H), 2.97-2.91 (m, 2H), 2.68 (dt, 1H), 2.52 (s, 3H), 2.37 (ddd, 1H), 2.27 (dd, 1H), 1.92 (dt, 1H). Compound **10b** was obtained as an oil (38%): R_f 0.41 (5% MeOH/CHCl₃); ¹H NMR δ 7.70 (t, 3H), 7.62 (s, 1H), 7.48-7.38 (m, 2H), 7.32 (d, 1H), 4.66 (dd, 2H), 4.19 (dd, 1H), 3.65 (s, 1H), 3.59 (s, 1H), 3.54 (s, 3H), 3.39-3.36 (m, 4H), 2.59 (s, 3H), 2.57-2.46 (m, 2H), 2.10 (ddd, 1H), 2.18 (dd, 1H), 1.53 (ddd, 1H).

EXAMPLE 17: 2 β -Carbomethoxy-3 β -(4-fluorophenyl)-6 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}octane (**9c**) and 2 β -carbomethoxy-3 α -(4-fluorophenyl)-6 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}octane (**10c**).

The title compounds were prepared as in the general procedure given above. Compound **9c** was obtained as an oil (31%): R_f 0.71 (10% Et₃N, 30% EtOAc, 60%/hexane); ¹H NMR δ 7.20-7.15 (m, 2H), 6.98-6.92 (m, 2H), 4.65 (s, 2H), 4.26 (dd, J = 7.4, 3.3 Hz, 1H) 3.76 (d, J = 6.6 Hz, 1H), 3.50 (s, 3H), 3.42 (s, 1H), 3.38 (s, 3H), 2.82-2.71 (m, 2H), 2.57-2.48 (m, 4H), 2.35 (ddd, J = 14.3, 7.4, 3.3 Hz, 1H), 2.19 (dd, J = 14.3, 7.4 Hz, 1H), 1.78 (m, 1H). Compound **10c** was obtained as an oil (23%): R_f 0.71 (10% Et₃N, 30% EtOAc, 60% hexane); ¹H NMR δ 7.15-7.11 (m, 2H), 6.98-6.91 (m, 2H), 4.64 (dd, 2H), 4.13 (dd, J = 7.1, 3.3 Hz, 1H), 3.60-3.53 (m, 4H), 3.40-3.31 (m, 5H), 2.57 (s, 3H), 2.54-2.26 (m, 3H), 2.12 (dd, J = 14.0, 7.1 Hz, 1H), 1.33 (ddd, J = 14.0, 10.9, 1.6 Hz, 1H).

EXAMPLE 17: 2 β -Carbomethoxy-3 β -phenyl-6 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}octane (9d**) and 2 β -carbomethoxy-3 α -phenyl-6 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}octane**

(**10d**).

The title compounds were prepared as in the general procedure given above. Compound **9d** obtained as an oil (28%): R_f 0.25 (5% MeOH/CHCl₃); ¹H NMR δ 7.29-7.13 (m, 5H), 4.66 (s, 2H), 4.27 (dd, J = 7.1, 3.3 Hz, 1H), 2.77 (m, 1H), 3.48 (s, 3H), 3.43 (s, 1H), 3.38 (s, 3H), 2.86 (t, J = 4.1 Hz, 1H), 2.79 (dt, J = 12.9, 4.9 Hz, 1H), 2.60-2.50 (m, 4H), 2.35 (ddd, J = 14, 6.8, 3.3 Hz, 1H), 2.20 (dd, J = 14.3, 7.4 Hz, 1H), 1.81 (dt, J = 12.4, 3.9 Hz, 1H). Compound **10d** obtained as an oil (25%): R_f 0.50 (5% MeOH/CHCl₃); ¹H NMR δ 7.29-7.14 (m, 5H), 4.64 (dd, 2H), 4.14 (dd, J = 7.1, 3.0 Hz, 1H), 3.59-3.57 (m, 4H), 3.48-3.32 (m, 5H), 2.57 (s, 3H), 2.50-2.37 (m, 2H), 2.29 (ddd, J = 14.6, 7.1, 3.0 Hz, 1H), 2.1 (dd, J = 14.3, 7.4 Hz, 1H), 1.4 (ddd, 1H).

EXAMPLE 18: 2 β -Carbomethoxy-3 β -(3,4-dichlorophenyl)-7 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}octane (11a**) and 2 β -carbomethoxy-3 α -(3,4-dichlorophenyl)-7 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}octane (**12a**).**

The title compounds were prepared as in the general procedure given above. Compound **11a** obtained as a yellow oil (37%): R_f 0.52 (5% MeOH/CHCl₃); ¹H NMR δ 7.35 (d, 1H), 7.30 (d, 1H), 7.10 (dd, 1H), 4.70 (dd, 2H), 4.35 (dd, 1H), 3.62 (s, 1H), 3.54 (m, 4H), 3.42 (s, 3H), 3.00 (m, 1H), 2.72-2.62 (m, 1H), 2.51-2.41 (m, 4H), 2.25 (ddd, 1H), 2.07 (dd, 1H), 1.59 (dt, 1H). Compound **12a** was obtained as a white solid (36%): R_f 0.67 (5% MeOH/CHCl₃); ¹H NMR δ 7.32 (d, 1H), 7.25 (d, 1H), 7.02 (dd, 1H), 4.66 (dd, 2H), 4.25 (dd, 1H), 3.62 (s, 3H), 3.48-3.32 (m, 6H), 2.54-2.47 (m, 4H), 2.43-2.33 (m, 1H), 2.20 (ddd, 1H), 2.00 (dd, 1H), 1.21 (dt, 1H).

100-99-98-97-96-95-94-93-92-91-90-89-88-87-86-85-84-83-82-81-80-79-78-77-76-75-74-73-72-71-70-69-68-67-66-65-64-63-62-61-60-59-58-57-56-55-54-53-52-51-50-49-48-47-46-45-44-43-42-41-40-39-38-37-36-35-34-33-32-31-30-29-28-27-26-25-24-23-22-21-20-19-18-17-16-15-14-13-12-11-10-9-8-7-6-5-4-3-2-1

EXAMPLE 19: *2 β -Carbomethoxy-3 β -(2-naphthyl)-7 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}octane (11b) and 2 β -carbomethoxy-3 α -(2-naphthyl)-7 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}octane (12b).*

The title compounds were prepared as in the general procedure given above. Compound **11b** was obtained as an oil (29%): R_f 0.41 (5% MeOH/CHCl₃); ¹H NMR δ 7.80-7.75 (m, 3H), 7.68 (s, 1H), 7.48-7.35 (m, 3H), 4.74 (dd, 2H), 4.44 (dd, 1H), 3.67-3.59 (m, 2H), 3.44 (s, 6H), 3.17 (t, 1H), 2.89 (dt, 1H), 2.69 (dt, 1H), 2.52 (s, 3H), 2.27 (ddd, 1H), 2.15 (dd, 1H), 1.72 (dt, 1H). Compound **12b** was obtained as an oil (26%): R_f 0.31 (5% MeOH/CHCl₃); ¹H NMR δ 7.78-7.72 (m, 3H), 7.67 (s, 1H), 6.95-6.88 (m, 3H), 4.67 (dd, 2H), 4.28 (dd, 1H), 3.58 (s, 3H), 3.53 (s, 1H), 3.45-3.37 (m, 5H), 2.50 (t, 1H), 2.47 (s, 3H), 2.42 (dt, 1H), 2.15 (ddd, 1H), 2.00 (dd, 1H), 1.23 (dt, 1H).

EXAMPLE 20: *2 β -Carbomethoxy-3 β -(4-fluorophenyl)-7 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}octane (11c) and 2 β -carbomethoxy-3 α -(4-fluorophenyl)-7 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}octane (12c).*

The title compounds were prepared as in the general procedure given above. Compound **11c** was obtained as an oil (35%): R_f 0.63 (EtOAc); ¹H NMR δ 7.22-7.18 (m, 2H), 6.98-6.91 (m, 2H), 4.71 (dd, 2H), 4.38 (dd, 1H), 3.62-3.57 (m, 2H), 3.50 (s, 3H), 3.42 (s, 3H), 2.99 (t, 1H), 2.87-2.78 (m, 1H), 2.57-2.48 (m, 4H), 2.22 (ddd, 1H), 2.06 (dd, 1H), 1.61 (dt, 1H). Compound **12c** was obtained as a solid (40%): R_f 0.36 (10% Et₃N, 30% EtOAc, 60% hexanes); ¹H NMR δ 7.16-7.10 (m, 2H), 6.97-6.91 (m, 2H), 4.66 (dd, 2H), 4.24 (dd, 1H), 3.59 (s, 3H), 3.46 (m, 1H), 3.39-3.33 (m, 5H), 2.51 (t, 1H), 2.48 (s, 3H), 2.38 (dt, 1H), 2.19 (ddd, 1H), 2.01 (dd, 1H), 1.24 (dt, 1H).

EXAMPLE 21: 2 β -Carbomethoxy-3 β -phenyl-7 β -methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (11d) and 2 β -carbomethoxy-3 α -phenyl-7 β -methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane

(12d).

The title compounds were prepared as in the general procedure given above. Compound **11d** was obtained as an oil (25%): R_f 0.15 (EtOAc); 1 H NMR δ 7.29-7.22 (m, 4H), 7.18-7.12 (m, 1H), 4.71 (dd, 2H), 4.37 (dd, 1H), 3.61-3.57 (m, 2H), 3.48 (s, 3H), 3.43 (s, 3H), 3.03 (t, 1H), 2.80-2.69 (dt, 1H), 2.60-2.48 (m, 4H), 2.25 (ddd, 1H), 2.07 (dd, 1H), 1.62 (dt, 1H). Compound **12d** was obtained as an oil (31%): R_f 0.50 (EtOAc); 1 H NMR δ 7.30-7.12 (m, 5H), 4.65 (dd, 2H), 4.24 (dd, 1H), 3.60 (s, 3H), 3.51-3.37 (m, 6H), 2.62-2.58 (m, 4H), 2.40 (dt, 1H), 2.20 (ddd, 1H), 2.03 (dd, 1H), 1.25 (dt, 1H).

EXAMPLE 22: General procedures for cleavage of MOM protecting group.

To a solution of MOM protected alcohol in anhydrous CH₂Cl₂ containing 4 Å molecular sieves, at 0 °C, was added TMSBr (10 eq). The solution was slowly allowed to warm up to 22 °C and stirred overnight. The reaction was quenched by slow addition of aq NaHCO₃ and the aqueous layer was exhaustively extracted with CH₂Cl₂. The extracts were combined and dried over K₂CO₃. The solvent was removed and residue was purified by flash column chromatography (10% Et₃N, 30-90% EtOAc, 60-0% hexanes) to give the product.

EXAMPLE 23: 2-Carbomethoxy-3-(3,4-dichlorophenyl)-6 β -hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (7a).

The procedure described above was followed. A white crystalline solid was obtained (71%): mp 94.0-96.0 °C; R_f 0.13 (10% Et₃N/EtOAc); 1 H NMR δ 7.39 (d, 1H), 7.21 (d, 1H), 6.95 (dd, 1H), 4.19 (m, 1H), 3.94 (d, J = 6.6 Hz, 1H), 3.53 (s, 3H), 3.23 (d, J = 5.8 Hz, 1H), 2.65 (dd, J = 19.5,

5.8 Hz, 1H), 2.54-2.48 (m, 4H), 2.25 (bs, 1H), 2.09-1.97 (m, 2H). Anal.
(C₁₆H₁₇Cl₂NO₃) C, H, N.

EXAMPLE 24: 2-Carbomethoxy-3-(2-naphthyl)-6 β -hydroxy-8-

5 methyl-8-azabicyclo{3.2.1}oct-2-ene (7b).

The procedure described above was followed to obtain a white powder (29%); mp 165.0-167.0 °C; R_f 0.15 (10% Et₃N/EtOAc); ¹H NMR δ 7.84-7.78 (m, 3H), 7.59 (s, 1H), 7.49-7.46 (m, 2H), 7.25-7.22 (m, 1H), 4.26 (dd, J = 7.4, 3.0 Hz, 1H), 4.00 (d, J = 6.3 Hz, 1H), 3.45 (s, 3H), 3.27 (d, J = 5.5 Hz, 1H), 2.77 (dd, J = 19.5, 5.8 Hz, 1H), 2.62-2.55 (m, 4H), 2.19 (d, J = 19.5 Hz, 1H), 2.08 (ddd, J = 13.5, 6.6, 2.7 Hz, 1H). Anal. (C₂₀H₂₁NO₃) C, H, N.

EXAMPLE 25: 2-Carbomethoxy-3-(4-fluorophenyl)-6 β -hydroxy-8-

15 methyl-8-azabicyclo{3.2.1}oct-2-ene (7c).

The procedure described above was followed to obtain a white crystalline solid (22%); mp 124.0-126.0 °C; R_f 0.31 (10% Et₃N/EtOAc); ¹H NMR δ 7.39-6.98 (m, 4H), 4.19 (dd, J = 7.1, 2.7 Hz, 1H), 3.94 (d, J = 6.6 Hz, 1H), 3.50 (s, 3H), 3.23 (d, J = 5.5 Hz, 1H), 2.66 (dd, J = 19.5, 5 Hz, 1H), 2.55-2.49 (m, 4H), 2.08-2.01 (m, 2H). Anal. (C₁₆H₁₈FNO₃) C, H, N.

EXAMPLE 26: 2-Carbomethoxy-3-phenyl-6 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}oct-2-ene (7d).

The procedure described above was followed to obtain a white crystalline solid (13%); mp 165.0-167.0 °C; R_f 0.22 (10% Et₃N/EtOAc); ¹H NMR δ 7.39-7.28 (m, 3H), 7.13-7.10 (m, 2H), 4.21 (dd, J = 7.4, 3.0 Hz, 1H), 3.94 (d, J = 6.6 Hz, 1H), 3.48 (s, 3H), 3.23 (d, J = 5.5 Hz, 1H), 2.70 (dd, J = 19.5, 5.5 Hz, 1H), 2.57-2.50 (m, 4H), 2.09 (d, J = 19.8 Hz, 1H), 2.07-2.01 (m, 1H). Anal. (C₁₆H₁₉NO₃) C, H, N.

EXAMPLE 27: 2-Carbomethoxy-3-(3,4-dichlorophenyl)-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}oct-2-ene (8a).

The procedure described above was followed. The product was

- 5 obtained as a white solid (34%): mp 130.4-132.4 °C; R_f 0.1 (EtOAc); ^1H NMR δ 7.37 (d, 1H), 7.19 (d, 1H), 6.95 (dd, 1H), 4.29 (m, 1H), 3.65 (s, 1H), 3.56 (s, 3H), 3.40 (m, 1H), 2.62 (dd, 1H), 2.48 (s, 3H), 2.08 (m, 2H), 1.80 (d, 1H). Anal. ($\text{C}_{16}\text{H}_{17}\text{Cl}_2\text{NO}_3$) C, H, N.

10 **EXAMPLE 28: (1S)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}oct-2-ene ((1S)-8a).**

This compound was obtained from (1S)-28 (*vide infra*) via the procedure described above: $[\alpha]^{21}\text{D} = -58^\circ$ ($c = 1.0$, CHCl₃), $[\alpha]^{21}\text{D} = -49^\circ$ ($c = 0.40$, MeOH) (>98% ee from ^1H NMR of (1S)-28) mp 130.4-131.8 °C.

15 **EXAMPLE 29: (1R)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}oct-2-ene ((1R)-8a).**

This compound was obtained from (1R)-2 (*vide infra*) via the procedure described above: $[\alpha]^{21}\text{D} +57^\circ$ ($c = 1.0$, CHCl₃) (>98% ee from ^1H NMR of (1R)-27) mp 129-131 °C.

EXAMPLE 30: 2-Carbomethoxy-3-(2-naphthyl)-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}oct-2-ene (8b).

The procedure described above was followed. The product was obtained as a white solid (57%): mp 164.2-165.2 °C; R_f 0.4 (5% Et₃N/EtOAc); ^1H NMR δ 7.80 (m, 3H), 7.58 (s, 1H), 7.48 (m, 2H), 7.26 (m, 1H), 4.35 (m, 1H), 3.79 (s, 1H), 3.44 (m, 4H), 2.74 (dd, 1H), 2.54 (s, 3H), 2.14 (m, 2H), 2.01 (d, 1H). Anal. ($\text{C}_{20}\text{H}_{21}\text{NO}_3$) C, H, N.

EXAMPLE 31: 2-Carbomethoxy-3-(4-fluorophenyl)-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}oct-2-ene (8c).

The procedure described above was followed. The product was

5 obtained as a yellow gum (58%): R_f 0.23 (10% Et₃N/EtOAc); ¹H NMR δ 7.15-6.96 (m, 4H), 4.30 (m, 1H), 3.75 (s, 1H), 3.50 (s, 3H), 3.41 (m, 1H), 2.85 (bs, 1H), 2.64 (dd, 1H), 2.48 (s, 3H), 2.08 (m, 2H), 1.85 (d, 1H). Anal. (C₁₆H₁₈FNO₃) C, H, N.

10 **EXAMPLE 32: 2-Carbomethoxy-3-phenyl-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}oct-2-ene (8d).**

The procedure described above was followed to provide a white

solid (62%): mp 113-114 °C; R_f 0.23 (10% Et₃N/EtOAc); ¹H NMR δ 7.36-7.30 (m, 3H), 7.15-7.08 (m, 2H), 4.31 (m, 1H), 3.73 (s, 1H), 3.51 (s, 3H), 3.41 (m, 1H), 2.66 (dd, 1H), 2.50 (s, 3H), 2.09 (m, 2H), 1.88 (d, 1H). Anal. (C₁₆H₁₉NO₃) C, H, N.

15 **EXAMPLE 33: 2 β -Carbamethoxy-3 β -(3,4-dichlorophenyl)-6 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane (14a).**

The procedure described above was followed to provide a white

solid (88%): mp 93.5-95.5 °C; R_f 0.18 (5% MeOH/CH₂Cl₂); ¹H NMR δ 7.33 (d, 1H), 7.28 (d, 1H), 7.06 (dd, 1H), 4.44 (m, 1H), 3.84 (m, 1H), 3.51 (s, 3H), 3.30 (m, 1H), 2.79 (m, 1H), 2.68 (m, 1H), 2.56 (s, 3H), 2.45 (dt, 1H), 2.32-2.18 (m, 2H), 1.76 (m, 1H). Anal. (C₁₆H₁₉Cl₂NO₃) C, H, N.

20 **EXAMPLE 34: 2 β -Carbamethoxy-3 β -(2-naphthyl)-6 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane (14b).**

The procedure described above was followed to provide a white

solid (89%): mp 84.0-86.0 °C; R_f 0.23 (10% MeOH/CH₂Cl₂); ¹H NMR δ 7.76 (t, 3H), 7.65 (s, 1H), 7.48-7.35 (m, 3H), 4.53 (m, 1H), 3.87 (m, 1H), 3.44 (s, 3H), 3.37 (m, 1H), 2.97-2.90 (m, 2H), 2.68 (dd, 1H), 2.60 (s, 3H), 2.32 (m, 2H), 1.93 (m, 1H), 1.78 (m, 1H). Anal. (C₂₀H₂₃NO₃) C, H, N.

REAGENTS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

EXAMPLE 35: 2β -Carbomethoxy- 3β -(4-fluorophenyl)- 6β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane (14c).

The procedure described above was followed to provide a white

- 5 solid (30%): mp 162.0-164.0 °C; R_f 0.21 (10% MeOH/CH₂Cl₂); ¹H NMR δ 7.71 (m, 2H), 6.95 (m, 2H), 4.48 (m, 1H), 3.83 (m, 1H), 3.50 (s, 3H), 3.31 (s, 1H), 2.82-2.71 (m, 2H), 2.57 (s, 3H), 2.52 (dt, 1H), 2.35-2.21 (m, 2H), 1.79-1.75 (m, 2H). Anal. (C₁₆H₂₀FNO₃) C, H, N.

10 **EXAMPLE 36:** 2β -Carbomethoxy- 3β -phenyl- 6β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane (14d).

The procedure described above was followed to provide a white

- solid (33%): mp 150.0-152.0 °C; R_f 0.13 (10% MeOH/CH₂Cl₂); ¹H NMR δ 7.2-7.14 (m, 5H), 4.50 (m, 1H), 3.85 (m, 1H), 3.48 (s, 3H), 3.36 (m, 1H), 15 2.88-2.75 (m, 2H), 2.60 (s, 3H), 2.55 (dd, 1H), 2.29 (m, 2H), 1.81 (m, 1H). Anal. (C₁₆H₂₁NO₃) C, H, N.

EXAMPLE 37: 2β -Carbomethoxy- 3β -(3,4-dichlorophenyl)- 7β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane (15a).

- 20 The procedure described above was followed to provide a colorless crystalline solid (68%): mp 185.5-186.5 °C; R_f 0.47 (10% Et₃N/EtOAc); ¹H NMR δ 7.32 (d, 1H), 7.29 (d, 1H), 7.07 (dd, 1H), 4.53 (m, 1H), 3.60 (m, 1H), 3.53 (s, 3H), 3.00 (t, J = 3.8 Hz, 1H), 2.68-2.64 (m, 1H), 2.55 (s, 3H), 2.50-2.44 (m, 1H), 2.23-2.08 (m, 2H), 1.78 (d, J = 3.8 Hz, 1H), 1.59 (m, 1H). Anal. (C₁₆H₁₉Cl₂NO₃) C, H, N.

EXAMPLE 38: (**1S**)- 2β -Carbomethoxy- 3β -(3,4-dichlorophenyl)- 7β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane (**(1S)-15a**).

Obtained from (**1S**)-**8a** (*vide infra*) $[\alpha]^{21}_D$ = +25° (c = 1.3, CHCl₃)

- 30 (>98% ee from ¹H NMR of (**1S**)-**28**) mp 185.5-186.5 °C.

EXAMPLE 39: (1*R*)-2 β -Carbomethoxy-3 β -(3,4-dichlorophenyl)-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane ((1*R*)-15a).

Obtained from (1*R*)-2 (*vide infra*) $[\alpha]^{21}_D = -26^\circ$ (c = 1.3, CHCl₃)

5 (>98% ee from ¹H NMR of (1*R*)-27) mp 186-187 °C.

EXAMPLE 40: 2 β -Carbomethoxy-3 β -(2-naphthyl)-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane (15b).

The procedure described above was followed to provide a white

10 crystalline solid: (78%); mp 207.5-208.5 °C; *R*_f 0.15 (10% MeOH/CHCl₃);
¹H NMR δ 7.76 (t, 3H), 7.65 (s, 1H), 7.47-7.35 (m, 3H), 4.63 (t, 1H), 3.66
(m, 1H), 3.58 (s, 1H), 3.45 (s, 3H), 3.17 (m, 1H), 2.97-2.87 (m, 1H), 2.67
(dt, 1H), 2.60 (s, 3H), 2.28-2.19 (m, 2H), 1.85 (bs, 1H), 1.76-1.70 (m, 1H).
Anal. (C₂₀H₂₃NO₃) C, H, N.

15 **EXAMPLE 41:** 2 β -Carbomethoxy-3 β -(4-fluorophenyl)-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane (15c).

The procedure described above was followed to obtain a white
crystalline solid (11%); mp 179.3-181.3 °C; *R*_f 0.53 (10% Et₃N/EtOAc);

20 ¹H NMR δ 7.18 (m, 2H), 6.96 (m, 2H), 4.59 (m, 1H), 3.67-3.61 (m, 2H),
3.50 (s, 3H), 3.03 (m, 1H), 2.79-2.50 (m, 5H), 2.20 (m, 2H), 1.61 (m, 1H).
Anal. (C₁₆H₂₀FNO₃) C, H, N.

25 **EXAMPLE 42:** 2 β -Carbomethoxy-3 β -phenyl-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane (15d).

The procedure described above was followed to obtain a white
crystalline solid (17%); mp 165.8-167.8 °C; *R*_f 0.13 (5% MeOH/CHCl₃);

30 ¹H NMR δ 7.30-7.13 (m, 5H), 4.58 (dd, J = 6.6, 4.1 Hz, 1H), 3.62 (m, 1H),
3.53 (s, 1H), 3.49 (s, 3H), 3.06 (m, 1H), 2.75 (m, 1H), 2.57 (m, 4H), 2.22-
2.11 (m, 2H), 1.64-1.59 (m, 1H). Anal. (C₁₆H₂₁NO₃) C, H, N.

EXAMPLE 43: 2 β -Carbomethoxy-3 α -(3,4-dichlorophenyl)-6 β -hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (17a).

The procedure described above was followed to obtain a white

- 5 powder (18%): mp 129.1–131.1 °C; R_f 0.57 (10% Et₃N/EtOAc); ¹H NMR δ 7.34 (d, 1H), 7.26 (d, 1H), 7.02 (dd, 1H), 4.25 (m, 1H), 3.64–3.61 (m, 4H), 3.48–3.35 (m, 1H), 3.20 (d, 1H), 2.65 (s, 3H), 2.38–2.08 (m, 4H), 1.90 (bs, 1H), 1.29 (dd, 1H). Anal. (C₁₄H₁₆Cl₂NO₃) C, H, N.

EXAMPLE 44: 2 β -Carbomethoxy-3 α -(2-naphthyl)-6 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane (17b).

The procedure described above was followed to provide a white solid (77%): mp 93.5–94.5 °C; R_f 0.45 (0.5% MeOH/CH₂Cl₂); ¹H NMR δ 7.77 (m, 3H), 7.63 (s, 1H), 7.45 (m, 2H), 7.32 (d, 2H), 4.29 (m, 1H), 3.68 (m, 2H), 3.57 (s, 3H), 3.23 (d, 1H), 2.70 (s, 3H), 2.63 (d, 1H), 2.41 (dt, 1H), 2.21 (m, 2H), 1.54 (dd, 1H). Anal. (C₂₀H₂₃NO₃) C, H, N.

EXAMPLE 45: 2 β -Carbomethoxy-3 α -(4-fluorophenyl)-6 β -hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (17c).

- 20 The procedure described above was followed to provide a yellow crystalline solid (39%): mp 148.0–150.0 °C; R_f 0.53 (10% MeOH/CH₂Cl₂); ¹H NMR δ 7.13 (dd, 2H), 6.97 (t, 2H), 4.26 (m, 1H), 3.64–3.59 (m, 4H), 3.43 (m 1H), 3.21 (d, 1H), 2.67 (s, 3H), 2.40–2.12 (m, 4H), 1.31 (dd, 1H). Anal. (C₁₆H₂₀FNO₃) C, H, N.

EXAMPLE 46: 2 β -Carbomethoxy-3 α -phenyl-6 β -hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (17d).

The procedure described above was followed to provide a white powder (22%): mp 138.0–140.0 °C; R_f 0.21 (10% Et₃N/EtOAc); ¹H NMR δ 7.30–7.12 (m, 5H), 4.24 (m, 1H), 3.66–3.60 (m, 4H), 3.48 (dd, J = 17.9, 9.1 Hz, 1H), 3.21 (d, J = 8.8 Hz, 1H), 2.68 (s, 3H), 2.49 (d, J = 9.1 Hz,

1H), 2.42-2.32 (m, 1H), 2.25-2.17 (m, 2H), 1.45-1.36 (m, 1H). Anal.
(C₁₆H₂₁NO₃) C, H, N.

EXAMPLE 47: 2 β -Carbomethoxy-3 α -(3,4-dichlorophenyl)-7 β -

5 hydroxy-8-methyl-8-azabicyclo{3.2.1}octane (**18a**).

The procedure described above was followed to provide a colorless solid (87%): mp 148.5-150 °C; R_f 0.18 (10% Et₃N, 40% EtOAc, 50% hexane); R_f 0.53 (10% Et₃N/EtOAc); ¹H NMR δ 7.31 (d, 1H), 7.26 (d, 1H), 7.25 (dd, 1H), 4.29 (m, 1H), 3.61 (s, 3H), 3.47-3.38 (m, 2H), 3.27 (s, 1H),
10 2.67 (s, 3H), 2.42-2.32 (m, 2H), 2.17-2.01 (m, 3H), 1.26 (dd, 1H). Anal.
(C₁₆H₁₉Cl₂NO₃) C, H, N.

EXAMPLE 48: (1S)-2 β -Carbomethoxy-3 α -(3,4-dichlorophenyl)-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane ((1S)-**18a**).

15 Obtained from (**1S**)-**8a**: $[\alpha]^{21}_D = -48^\circ$ (c = 1.0, CHCl₃); $[\alpha]^{21}_D = -36^\circ$
(c = 0.40, MeOH) (>98% ee from ¹H NMR of (**1S**)-**27**) mp 148.5-150 °C.

EXAMPLE 49: (1R)-2 β -Carbomethoxy-3 α -(3,4-dichlorophenyl)-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane ((1R)-**18a**).

20 Obtained from (**1R**)-**2**: $[\alpha]^{21}_D = +47^\circ$ (c = 1.0, CHCl₃) (>98% ee
from ¹H NMR of (**1R**)-**27**) mp 149-150 °C.

EXAMPLE 50: 2 β -Carbomethoxy-3 α -(2-naphthyl)-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane (**18b**).

25 The procedure described above was followed to provide a yellow crystalline solid (62%): mp 140.1-141.9 °C; R_f 0.20 (5% MeOH/CH₂Cl₂);
¹H NMR δ 7.82-7.76 (m, 3H), 7.63 (s, 1H), 7.49-7.41 (m, 2H), 7.32 (d,
1H), 4.33 (m, 1H), 3.64 (m, 1H), 3.57 (s, 3H), 3.50 (m, 1H), 3.32 (s, 1H),
2.73 (s, 3H), 2.67 (d, 1H), 2.20-2.08 (m, 3H), 1.53-1.46 (m, 1H). Anal.
30 (C₂₀H₂₃NO₃) C, H, N.

EXAMPLE 51: 2 β -Carbomethoxy-3 α -(4-fluorophenyl)-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane (18c).

The procedure described above was followed to obtain a white

- 5 crystalline solid (47%): mp 177.2-179.0 °C; R_f 0.12 (EtOAc); ^1H NMR δ 7.18-7.10 (m, 2H), 6.99-6.93 (m, 2H), 4.29 (m, 1H), 3.59 (s, 3H), 3.51-3.38 (m, 2H), 3.26 (s, 1H), 2.70 (s, 3H), 2.47-2.35 (m, 2H), 2.18-2.00 (m, 2H), 1.29 (m, 1H). Anal. ($\text{C}_{16}\text{H}_{20}\text{FNO}_3$) C, H, N.

10 **EXAMPLE 52: 2 β -Carbomethoxy-3 α -phenyl-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane (18d).**

The procedure described above was followed to provide a white

- powder (26%): mp 165.0-167.0 °C; R_f 0.19 (5% MeOH/CH₂Cl₂); ^1H NMR δ 7.31-7.15 (m, 5H), 4.29 (m, 1H), 3.59 (s, 3H), 3.52-3.42 (m, 2H), 3.29 (s, 1H), 2.71 (s, 3H), 2.54-2.36 (m, 2H), 2.18-2.02 (m, 2H), 1.39 (dd, 1H). Anal. ($\text{C}_{16}\text{H}_{21}\text{NO}_3$) C, H, N.

Preparation of 7 α and 6 α -hydroxy tropanes (30).

20 **EXAMPLE 53: 2 β -Carbomethoxy-3 α -(3,4-dichlorophenyl)-7 α -benzoyloxy-8-methyl-8-azabicyclo{3.2.1}octane (29b).**

To a solution of 2 β -carbomethoxy-3 α -(3,4-dichlorophenyl)-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane, **18a** (0.46 g, 1.34 mmol) in THF (20 mL) with benzoic acid (0.49 g, 4.0 mmol) and

- 25 triphenylphosphine (0.70 g, 2.68 mol) was added diethyl azodicarboxylate (DEAD) (0.46 g, 2.68 mmol) dropwise at 0 °C. The reaction was kept stirring overnight at 22 °C. The solvent was removed and the residue was purified by a flash column chromatography (30% hexanes in EtOAc) to give the product as a white solid (0.43 g, 72%). R_f 30 0.53 (30% hexane, 70% EtOAc); ^1H NMR δ 8.06 (dd, 2H), 7.65 (d, 1H), 7.49 (t, 2H), 7.32 (d, 1H), 7.28 (d, 1H), 7.07 (dd, 1H), 5.68 (m, 1H), 3.73

(d, 1H], 3.55 (s, 3H), 3.48-3.31 (m, 2H), 3.10 (d, 1H), 3.01-2.85 (m, 1H), 2.53-2.47 (m, 4H), 1.64 (dd, 1H), 1.41 (dt, 1H).

EXAMPLE 54: *2 β -Carbomethoxy-3 α -(3,4-dichlorophenyl)-6 α -*

benzoyloxy-8-methyl-8-azabicyclo{3.2.1}octane (29a).

2 β -Carbomethoxy-3 α -(3,4-dichlorophenyl)-6 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane, **17a** (0.23 g) was treated as described above for the 7-hydroxy compound. A white solid was obtained (0.19 g, 63%): R_f 0.77 (30% hexane, 70% EtOAc); 1 H NMR δ 8.14-8.02 (m, 2H), 7.63-7.46 (m, 3H), 7.29 (dd, 2H), 7.05 (dd, 1H), 5.60 (m, 1H), 3.68-3.60 (m, 4H), 3.45-3.35 (m, 2H), 3.11-2.93 (m, 1H), 2.63-2.49 (m, 4H), 2.30-2.15 (m, 1H), 1.85-1.95 (m, 2H).

EXAMPLE 55: *2 β -Carbomethoxy-3 α -(3,4-dichlorophenyl)-7 α -*

hydroxy-8-methyl-8-azabicyclo{3.2.1}octane (30b).

To a solution of 2 β -carbomethoxy-3 α -(3,4-dichlorophenyl)-7 α -benzoyloxy-8-methyl-8-azabicyclo{3.2.1}octane **29b** (0.43 g, 0.95 mmol) in THF (26 mL) was added LiOH (0.085 g, 1.9 mmol in 5 ml H₂O). The resulting solution was stirred for 5 h at 22 °C and quenched with aqueous HCl (3%). The THF was removed and the aqueous layer was extracted with CHCl₃ (6 x 20 mL). The organic layers were combined and dried over K₂CO₃. The solvent was removed and the residue was purified by column chromatography (10% Et₃N in EtOAc) to afford the product as a white gum which solidified slowly upon standing (0.19 g, 26%): mp 121-123 °C; R_f 0.41 (10% Et₃N/EtOAc); 1 H NMR δ 7.36 (d, 1H), 7.33 (d, 1H), 7.12 (dd, 1H), 4.79 (ddd, J = 9.9, 6.0, 3.8 Hz, 1H), 3.59 (s, 3H), 3.46-3.33 (m, 3H), 3.24 (t, J = 7.9 Hz, 1H), 2.83-2.68 Hz (m, 1H), 2.55-2.43 (m, 4H), 1.40-1.25 (m, 2H). Anal. (C₁₆H₁₉Cl₂NO₃) C, H, N.

EXAMPLE 56: 2 β -Carbomethoxy-3 α -(3,4-dichlorophenyl)-6 α -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane (30a).

2 β -Carbomethoxy-3 α -(3,4-dichlorophenyl)-6 α -benzoyloxy-8-

- 5 methyl-8-azabicyclo{3.2.1}octane **29a** (0.18 g, 0.39 mmol) was treated as described above and a white solid was obtained (51 mg, 38%): mp 161.2-162.2 °C; R_f 0.26 (10% Et₃N in EtOAc); ¹H NMR δ 7.35 (d, 1H), 7.34 (d, 1H), 7.11 (dd, 1H), 4.72 (m, 1H), 3.57 (s, 3H), 3.37-3.25 (m, 3H), 2.88-2.77 (m, 1H), 2.50 (d, 1H), 2.42 (s, 3H), 2.20-1.97 (m, 2H), 1.52 (dd, 1H).
10 Anal. (C₁₆H₁₉Cl₂NO₃) C, H, N.

Oxidation of 7-hydroxy tropanes to 7-ketones (19 and 20).

EXAMPLE 57: 2 β -Carbomethoxy-3 α -(3,4-dichlorophenyl)-8-

- 15 methyl-8-azabicyclo{3.2.1}oct-7-one (20).
- A solution of 2 β -carbomethoxy-3 α -(3,4-dichlorophenyl)-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane **18** (0.20 g, 0.58 mmol) in CH₂Cl₂ (5 ml) containing *N*-methylmorpholine *N*-oxide (1.5 eq) and 4 Å molecular sieves (0.5 g; powder) was stirred for 10 min at 22 °C under N₂ and then treated with tetra-*n*-propylammonium perruthenate (10% molar eq). The resulting solution was stirred overnight. The solvent was removed and the residue was purified by flash column chromatography (10% Et₃N, 30% EtOAc, 60% hexanes) to afford a white solid (0.16 g, 80%): mp 163.5-164.5 °C; R_f 0.47 (10% Et₃N, 30% EtOAc, 60% hexanes);
20 ¹H NMR δ 7.34 (d, 1H), 7.29 (d, 1H), 7.02 (dd, 1H), 3.68-3.60 (m, 5H), 3.27 (m, 1H), 2.84 (dd, J = 7.9, 1.9 Hz, 1H), 2.59-2.30 (m, 2H), 2.44 (s, 3H), 1.92 (d, J = 18.4 Hz, 1H), 1.52 (ddd, J = 14.0, 8.5, 1.9 Hz, 1H). Anal. (C₁₆H₁₇Cl₂NO₃) C, H, N.

EXAMPLE 58: 2 β -Carbomethoxy-3 β -(3,4-dichlorophenyl)-8-methyl-8-azabicyclo{3.2.1}oct-7-one (19).

2 β -Carbomethoxy-3 β -(3,4-dichlorophenyl)-7 β -hydroxy-8-methyl-

- 5 8-azabicyclo{3.2.1}octane, **15** was treated as described above and the product was obtained as a white solid (170 mg, 81%): mp 84.4-86.4 °C;
 R_f 0.60 (10% Et₃N, 30% EtOAc, 60% hexanes); ¹H NMR δ 7.35 (d, 1H),
7.32 (d, 1H), 7.09 (dd, 1H), 3.75 (dt, J = 5.2, 1.3 Hz, 1H), 3.56 (s, 3H),
3.34 (s, 1H), 3.22 (t, J = 3.8 Hz, 1H), 2.98 (dt, J = 4.7, 12.9 Hz, 1H), 2.84
10 (dt, J = 12.7, 3.3 Hz, 1H), 2.73 (dd, J = 18.7, 7.4 Hz, 1H), 2.39 (s, 3H),
2.12 (d, J = 18.7 Hz, 1H), 1.86 (dt, J = 12.1, 3.3 Hz, 1H). Anal.
(C₁₆H₁₇Cl₂NO₃) C, H, N.

Preparation of 2 β -ethyl ketone tropanes (23 and 26).

15 **EXAMPLE 59:** 2 β -Carbo-N-methoxy-N-methylamino-3 α -(3,4-dichlorophenyl)-7 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}octane (**24**) (Weinreb amide).

- To a solution of *N,O*-dimethylhydroxylamine hydrochloride (0.34 g, 3.48 mmol) in CH₂Cl₂ (10 mL) was added Al(CH₃)₃ dropwise at -12 °C (glycol-dry ice bath) under N₂. The resulting solution was stirred for 10 min. At -12 °C before the cooling bath was removed and the reaction stirred at 22 °C for 30 min. The reaction was cooled to -12 °C and a solution of 2 β -carbomethoxy-3 α -(3,4-dichlorophenyl)-7 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}octane, **12a** (0.45 g, 1.16 mmol) in CH₂Cl₂ (4 mL) was transferred by cannula into the reaction flask and the reaction was stirred for 1 h at -12 °C and then 2 h at 22 °C. Rochelle's salt solution (potassium sodium tartrate saturated in water) (~ 1 ml) was added and the mixture was stirred vigorously. Water was added to dissolve some solid salt and the aqueous layer was extracted with CHCl₃ (6 x 20 mL). The organic layers were combined and dried over K₂CO₃. The solvent was removed. The residue was purified by

passing it through a short silica gel column (10% Et₃N in EtOAc) to afford a white solid (0.47 g, 89%). *R*_f 0.39 (10% Et₃N, 30% EtOAc, 60% hexane); ¹H NMR δ 7.29 (d, 1H), 7.26 (d, 1H), 7.05 (dd, 1H), 4.67 (dd, J = 3.6, 6.8 Hz, 2H), 4.37 (dd, J = 7.1, 3.3 Hz, 1H), 3.56 (s, 3H), 3.54-3.46 (m, 2H), 3.14 (m, 1H), 3.10 (s, 3H), 2.65 (d, J = 11.3 Hz, 1H), 2.54 (s, 3H), 2.48-2.37 (m, 1H), 2.26-2.18 (m, 1H), 2.02 (dd, J = 14.0, 7.4 Hz, 1H), 1.16-1.07 (m, 1H).

EXAMPLE 60: 2β-Carbo-N-methoxy-N-methylamine-3β-(3,4-dichlorophenyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (21) (Weinreb amide).

The starting material 11a (0.47 g, 1.2 mmol) was treated as for the 3α compound shown above. A solid was obtained (0.31 g, 61%): *R*_f 0.45 (10% Et₃N, 30% EtOAc, 60% hexane); ¹H NMR δ 7.31 (d, 1H), 7.31 (d, 1H), 7.11 (dd, 1H), 4.69 (s, 2H), 4.34 (dd, J = 7.7, 3.6 Hz, 1H), 3.66 (s, 3H), 3.61-3.58 (m, 2H), 3.42 (s, 3H), 3.28 (m, 1H), 3.05 (s, 3H), 2.74-2.68 (m, 2H), 2.49 (s, 3H), 2.28-2.20 (m, 1H), 2.09-2.02 (m, 1H), 1.60-1.56 (m, 1H).

EXAMPLE 61: 1-{3α-(3,4-Dichlorophenyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-yl}propan-1-one (25).

To a solution of 2β-carbo-N-methoxy-N-methylamino-3α-(3,4-dichlorophenyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane, 24 (0.47 g, 1.13 mmol) in THF (anhydrous, 15 mL) was added ethyl magnesium bromide (3.4 ml, 1M in THF) dropwise at 0°C under N₂. The reaction was slowly warmed to 22 °C and stirred overnight. The reaction was then quenched with aqueous sat. NH₄Cl solution. The THF was replaced by CH₂Cl₂. The aqueous layer was extracted by CHCl₃ (6 x 20 mL). The organic solution was dried over K₂CO₃ and solvent was removed to afford a white solid (0.45 g, ~ 100%). The sample was used for the next reaction without further purification. *R*_f 0.67 (10% Et₃N, 30% EtOAc, 60% hexane); ¹H NMR δ 7.30 (d, 1H), 7.23 (d, 1H), 7.00 (dd, 1H), 4.68

(dd, $J = 8.5, 1.7$ Hz, 2H), 4.24 (dd, $J = 7.4, 3.6$ Hz, 1H), 3.47-3.31 (m, 5H), 3.20 (s, 1H), 2.56-2.31 (m, 6H), 2.27-1.99 (m, 3H), 1.22-1.13 (m, 1H), 0.96 (t, $J = 7.1$ Hz, 3H).

5 **EXAMPLE 62:** 1-{3 β -(3,4-Dichlorophenyl)-7 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}oct-2-yl}propan-1-one (**22**).

Weinreb amide **21** (0.31 g, 0.74 mmol) was treated as described above to obtain a white solid product (0.27 g, 95%). R_f 0.71 (10% Et₃N, 30% EtOAc, 60% hexane); ¹H NMR δ 7.30 (d, 1H), 7.27 (d, 1H), 7.06 (dd, 1H), 4.72 (s, 2H), 4.31 (dd, $J = 7.4, 3.6$ Hz, 1H), 3.59-3.54 (m, 2H), 3.44 (s, 3H), 3.12 (m, 1H), 2.68-2.66 (m, 1H), 2.52-2.40 (m, 5H), 2.30-2.17 (m, 2H), 2.05 (dd, $J = 14.3, 7.7$ Hz, 1H), 1.62-1.55 (m, 1H), 0.92 (t, $J = 7.1$ Hz, 3H).

15 **EXAMPLE 63:** 1-{3 α -(3,4-Dichlorophenyl)-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}oct-2-yl}propan-1-one (**26**).

The deprotection of the MOM group of **25** was carried out by the general method described earlier. 2 β -(1-Propanoyl)-3 α -(3,4-dichlorophenyl)-7 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}octane (0.27 g) was used and the product was obtained as a white solid (0.23 g, 76%): mp 113.1-114.1 °C; R_f 0.25 (10% Et₃N, 30% EtOAc, 60% hexanes); ¹H NMR δ 7.32 (d, 1H), 7.22 (d, 1H), 6.97 (dd, 1H), 4.27 (m, 1H), 3.50-3.41 (m, 2H), 3.06 (s, 1H), 2.67 (s, 3H), 2.67 (s, 3H), 2.52-2.32 (m, 3H), 2.18-2.01 (m, 3H), 1.25 (m, 1H), 0.94 (t, $J = 7.4$ Hz, 3H). Anal.

25 (C₁₇H₂₁Cl₂NO₂) C, H, N, Cl.

EXAMPLE 64: 1-{3 β -(3,4-Dichlorophenyl)-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}oct-2-yl}propan-1-one (**23**).

The deprotection of the MOM group of **22** was carried out by the general method described earlier. 2 β -(1-Propanoyl)-3 β -(3,4-dichlorophenyl)-7 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}octane (0.28 g) was used and the product was obtained as a white solid (0.18 g,

73%): mp 195.5–196.5 °C; R_f 0.39 (10% Et₃N, 30% hexanes, 60% EtOAc); ¹H NMR δ 7.31 (d, 1H), 7.26 (d, 1H), 7.05 (dd, 1H), 4.59 (p, J = 3.3 Hz, 1H), 3.60 (m, 1H), 3.52 (m, 1H), 3.10 (dd, J = 4.4, 3.3 Hz, 1H), 2.65–2.41 (m, 6H), 2.26 (q, J = 7.4 Hz, 2H), 2.24–2.09 (m, 2H), 1.86 (d, J = 3.8 Hz, 1H), 0.92 (t, J = 7.4 Hz, 3H). Anal. (C₁₇H₂₁Cl₂NO₂) C, H, N.

Preparation of 7 and 6-hydroxy difluoropines (32).

EXAMPLE 65: 2β-Carbomethoxy-3α-hydroxy-7β-

10 **methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (31b).**

To a solution of 2β-carbomethoxy-7β-methoxymethoxy-8-methyl-3-oxo-8-azabicyclo[3.2.1]octane **1b** (1.0 g, 3.89 mmol) in MeOH (100 mL) was added NaBH₄ (0.36 g, 9.72 mmol) at –78 °C. The mixture was kept in a freezer (~25 °C) for 3 days. The reaction was quenched with H₂O (40 mL) and MeOH was removed. The aqueous layer was extracted with CH₂Cl₂ (6 x 20 mL). The extracts were combined and dried over K₂CO₃ and solvent was removed. The residue was purified by gradient flash chromatography (5% MeOH in CHCl₃ to 10% MeOH in CHCl₃) to give the product as a yellow oil (0.53 g, 52%). R_f 0.21 (10% MeOH/CHCl₃); ¹H

20 NMR δ 4.67–4.58 (m, 3H), 4.29 (t, 1H), 3.77 (s, 3H), 3.52 (m, 1H), 3.34 (s, 3H), 3.31–3.23 (m, 2H), 2.93 (t, 1H), 2.58 (dd, 1H), 2.54 (s, 3H), 2.06–1.98 (m, 2H), 1.66 (d, 1H).

EXAMPLE 66: 2β-Carbomethoxy-3α-hydroxy-6β-

25 **methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (31a).**

2β-Carbomethoxy-6β-methoxymethoxy-8-methyl-3-oxo-8-azabicyclo[3.2.1]octane **1a** (1.0 g) was treated as described above to obtain the product as an oil (0.53 g, 52%). R_f 0.21 (10% MeOH/CHCl₃); ¹H NMR δ 4.64 (s, 2H), 4.59 (dd, 1H), 4.28 (m, 1H), 3.74 (s, 3H), 3.59 (m, 1H), 3.46 (s, 1H), 3.36 (s, 3H), 3.17 (s, 1H), 2.89 (m, 1H), 2.63–2.55 (m, 4H), 2.09–1.95 (m, 2H), 1.76 (d, 1H).

EXAMPLE 67: 2 β -Carbomethoxy-3 α -bis(fluorophenyl)methoxy-7 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane (32b).

A solution of 2 β -carbomethoxy-3 α -hydroxy-7 β -methoxymethoxy-

- 5 8-methyl-8-azabicyclo{3.2.1}octane **31b** (0.52 g, 2.04 mmol) and 4,4'-difluorobenzhydrol (0.53 g, 2.22 mmol) in CH₂Cl₂ (50 mL) with *p*-toluenesulfonic acid (0.39 g, 2.04 mmol) was placed in a round bottom flask equipped with a soxhlet condenser in which a thimble filled with molecular sieves (3 Å) was placed. The reaction was heated to reflux
10 overnight during which time the molecular sieves were replaced with fresh sieves several times. The reaction was quenched with sat NaHCO₃ and the aqueous layer was extracted with CH₂Cl₂. The extracts were combined and dried over K₂CO₃ and solvent was removed on a rotary evaporator. The residue was purified by column chromatography (5%
15 MeOH in EtOAc to 10% MeOH in EtOAc) to afford the desired product as a white solid (0.21 g, 22%): mp 150–152 °C; *R*_f 0.09 (5% MeOH, EtOAc);
¹H NMR δ 7.25 (dd, 4H), 6.99 (m, 4H), 5.45 (s, 1H), 4.42 (dd, *J* = 7.1, 2.8 Hz, 1H), 4.24 (t, *J* = 4.4 Hz, 1H), 3.71 (s, 3H), 3.64 (m, 1H), 3.35 (m, 1H), 2.97 (s, 1H), 2.78 (s, 1H), 2.61 (s, 3H), 2.53 (dd, *J* = 13.1, 7.4 Hz, 1H),
20 2.15 (m, 1H), 2.02 (m, 1H), 1.69 (d, *J* = 14.3 Hz, 1H). Anal.
(C₂₃H₂₅F₂NO₄) C, H, N.

EXAMPLE 68: 2 β -Carbomethoxy-3 α -bis(4-fluorophenyl)methoxy-6 β -hydroxy-8-methyl-8-azabicyclo{3.2.1}octane (32a).

- 25 2 β -Carbomethoxy-3 α -hydroxy-6 β -methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}octane **31a** (0.54 g, 2.10 mmol) was treated as described above and the product was obtained as a white foam. (0.17 g, 17%): *R*_f 0.32 (10% MeOH/CHCl₃); ¹H NMR δ 7.25 (dd, *J* = 8.5, 5.8 Hz, 4H), 6.99 (dt, *J* = 8.5, 0.8 Hz, 4H), 5.34 (s, 1H), 4.48 (dd, *J* = 7.2, 2.8 Hz, 1H), 4.20 (m, 1H), 3.73 (s, 3H), 3.61 (d, *J* = 8.0 Hz, 1H), 3.26 (s, 1H), 3.17 (s, 1H), 2.88 (bs, 1H), 2.58 (s, 3H), 2.48 (dd, *J* = 13.7, 7.14 Hz, 1H), 2.07 (ddd, *J*

= 14.0, 7.4, 2.7 Hz, 1H], 1.97 (d, J = 16.8 Hz, 1H). Anal. (C₂₃H₂₅F₂NO₄) C, H, N.

Resolution of 7-hydroxy tropanone.

5

EXAMPLE 69: (1*R*)-2-Carbomethoxy-3-(1'S)-camphanyl-7β-methoxymethoxy-8-methyl-8-azabicyclo{3.2.1}oct-2-ene (27).

To a solution of racemic 2β-carbomethoxy-7β-methoxymethoxy-8-methyl-3-oxo-8-azabicyclo{3.2.1}octane **2b** (7.1 g, 27.6 mmol) in THF

10 (anhydrous, 100 mL) cooled at -78 °C, NaN(TMS)₂ (35.9 mL, 1 M in THF) was added dropwise by syringe. The resulting solution was stirred for 45

min. At -78 °C and (1*S*)-(-)-camphanic chloride (8.3 g, 38.6 mmol) was added. The solution was stirred overnight, during which time it slowly

warmed up to 22 °C. The reaction was quenched with sat. NaHCO₃ (20

15 mL). The THF was replaced with CH₂Cl₂. The organic layer was separated and aqueous layer was back extracted with CH₂Cl₂ (6 x 20 mL). The organic extracts were combined and dried over K₂CO₃ and solvent was removed. The residue was purified by flash chromatography (5% MeOH

in EtOAc) to afford the product (7.75 g, 64%) as a yellow oil which

20 solidified upon standing for 3 days. NMR showed two diastereoisomers in the sample. The (1*R*,1'S) diastereoisomer was separated by recrystallization (5 times) from benzene/heptane to give diasteromerically pure **27** as a white solid (1.4 g, 36%, > 98% de by ¹H NMR). Despite repeated efforts, the (1*S*,1'S) diastereomer could not be isolated pure. The

25 ¹H NMR of the diastereomeric mixture is provided below. Of particular interest is the region 1.2-0.7 ppm as in benzene-d₆ the two diastereomers show different chemical shifts. ¹H NMR (C₆D₆) δ 4.70 (m, 1H), 4.55 (m, 1H), 4.19 (m, 1H), 4.11 (m, 1H), 3.28 (m, 3H), 3.21 (m, 3H), 2.9 (m, 1H), 2.35 (m, 3H), 2.34-2.18 (m, 2H), 2.11-2.02 (m, 2H), 1.66 (m, 1H), 1.29-

30 1.21 (m, 4H), 1.026 (s, 3H, 1*S*,1'S), 0.992 (s, 3H, 1*R*,1'S), 0.897 (s, 3H, 1*S*,1'S), 0.890 (s, 3H, 1*R*,1'S), 0.817 (s, 3H, 1*S*,1'S), 0.803 (s, 3H, 1*R*,1'S).

The (*1R,1'S*) product of recrystallization **27** was diastereomerically pure (>98% de) as confirmed by the complete absence of the (*1S,1'S*)-diastereomer at 1.015 ppm. R_f 0.42 (5% MeOH/EtOAc); ^1H NMR (C_6D_6) δ 4.70 (d, J = 6.6 Hz, 1H), 4.55 (d, J = 6.6 Hz, 1H), 4.19 (dd, J = 7.4, 2.2 Hz, 1H), 4.11 (s, 1H), 3.28 (s, 3H), 3.21 (s, 3H), 2.9 (m, 1H), 2.35 (s, 3H), 2.34-2.18 (m, 2H), 2.11-2.02 (m, 2H), 1.66 (dd, J = 13.4, 7.4 Hz, 1H), 1.29-1.21 (m, 4H), 0.98 (s, 3H), 0.89 (s, 3H), 0.78 (s, 3H).

EXAMPLE 70: (*1R*)-7 β -methoxymethoxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo[3.2.1]octane ((*1R*)-2).

A solution of (*1R*)-2-carbomethoxy-3-(*1'S*)-camphanyl-7 β -hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene **27** (1.40 g, 3.20 mmol) in THF (50 mL) was treated with LiOH aqueous solution (0.26 g, 6.4 mmol, 16 mL H₂O) and the resulting solution was stirred at 22 °C for 3 h. The THF was removed *in vacuo* and K₂CO₃ (8 g) was added to the aqueous solution which was exhaustively extracted with CH₂Cl₂. The CH₂Cl₂ extracts were combined and dried over K₂CO₃. Solvent was removed to obtain a white solid (**1R-2**) (0.89 g) that was used for the ensuing steps without further purification. ^1H NMR δ 4.67 (d, 1H), 4.54 (d, 1), 3.98 (s, 1H), 3.93 (dd, 1H), 3.30 (s, 3H), 3.21 (s, 3H), 2.92 (dd, 1H), 2.43 (m, 1H), 2.50 (dd, 1H), 2.21 (s, 3H), 2.05 (dd, 1H), 1.51 (dd, 1H), 1.42 (d, 1H).

EXAMPLE 71: (*1S*)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-7 β -(*1'S*)-camphanyloxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (28).

A solution of racemic 2-carbomethoxy-3-(3,4-dichlorophenyl)-7 β -hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene **8a** (11.1 g, 32 mmol) in CH₂Cl₂ (250 mL) with Et₃N (6.8 mL, 48.7 mmol) was treated with 1*S*(--)-camphanic chloride (10.5 g, 48.7 mmol) at 0 °C. The resulting solution was stirred overnight at 22 °C and then quenched with NaHCO₃ (sat.). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The organic layers were combined and dried over MgSO₄. The solvent was removed and the crude product containing

the two diastereoisomers was separated by two consecutive gravity columns (10% Et₃N, 30% EtOAc, 60% hexanes). The pure (1*S*,1'*S*) product **28** (2.4 g) was obtained as a yellow solid. A further 1.8 g was obtained as a mixture of diastereomers: *R*_f(one elution: both

- 5 diastereomers run together) 0.14 (10% Et₃N, 30% EtOAc, 60% hexane); *R*_f(two elutions) (1*S*,1'*S*) 0.25 (1*R*,1'*S*) 0.18 (10% Et₃N, 30% EtOAc, 60% hexane).

The ¹H NMR of **28** showed no trace of the (1*R*,1*S*) diastereomer and was therefore diastereomerically pure (de>98%). ¹H NMR (C₆D₆) δ

- 10 7.08 (d, 1H), 7.02 (d, 1H), 6.47 (dd, J = 8.3, 2.2 Hz, 1H), 5.34 (dd, J = 7.4, 2.2 Hz, 1H), 4.16 (s, 1H), 3.15 (s, 3H), 2.89 (dd, J = 6.9, 4.7 Hz, 1H), 2.19 (s, 3H), 2.17-2.07 (m, 2H), 1.98 (dd, J = 18.4, 5.2 Hz, 1H), 1.82-1.65 (m, 2H), 1.25-1.09 (m, 3H), 0.92 (s, 3H), 0.82 (s, 3H), 0.72 (s, 3H).

- 15 **EXAMPLE 72:** (1*R*)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-7β-camphanoyl-8-methyl-8-azabicyclo{3.2.1}oct-2-ene ((1*R*)-**28**).

In order to confirm that the above compound is 1*S* configured, a similar reaction was carried out by using the 1*R* ene compound. ¹H NMR (C₆D₆) δ 7.11 (d, 1H), 7.05 (d, 1H), 6.52 (dd, 1H), 5.36 (dd, J = 7.4, 2.2 Hz, 1H), 4.18 (s, 1H), 3.17 (s, 3H), 2.94 (dd, J = 6.9, 4.7 Hz, 1H), 2.20 (s, 3H), 2.16-1.98 (m, 3H), 1.84 (dd, J = 14.3, 7.6 Hz, 1H), 1.74-1.65 (m, 1H), 1.25-1.10 (m, 3H), 0.89 (s, 3H), 0.83 (s, 3H), 0.75 (s, 3H).

EXAMPLE 73: Single-Crystal X-ray Analysis of (1*R*)-**8a**.

- 25 Monoclinic crystals of the purified (1*R*)-**8a** were obtained from CH₂Cl₂/heptane. A representative crystal was selected and a data set was collected at room temperature. Pertinent crystal, data collection and refinement parameters: crystal size, 0.66 x 0.50 x 0.22 mm; cell dimensions, *a* = 18.382 (1) Å, *b* = 6.860 (1) Å, *c* = 16.131 (1) Å, α = 90°, β = 124.65 (1) °, γ = 90°; formula, C₁₆H₁₇Cl₂NO₃; formula weight = 342.21; volume = 1673.3 (2) Å³; calculated density = 1.358 g cm⁻³; space group = C2; number of reflections = 1749 of which 1528 were

considered independent (R int = 0.0300). Refinement method was full-matrix least-squares on F^2 . The final R -indices were $\{I > 2\sigma(I)\}$ $R1 = 0.0364$, $wR2 = 0.0987$.

5 **EXAMPLE 74: Single-Crystal X-ray Analysis of (1*R*)-18a.**

Monoclinic crystals of the purified (1*R*)-18a were obtained from ethyl CH_2Cl_2 /heptane. A representative crystal was selected and a data set was collected at room temperature. Pertinent crystal, data collection and refinement parameters: crystal size, $0.72 \times 0.30 \times 0.14$ mm; cell dimensions, $a = 5.981$ (1) Å, $b = 7.349$ (1) Å, $c = 18.135$ (1) Å, $\alpha = 90^\circ$, $\beta = 96.205$ (6) °, $\gamma = 90^\circ$; formula, $\text{C}_{16}\text{H}_{19}\text{Cl}_2\text{NO}_3$; formula weight = 344.22; volume = 792.29 (12) Å³; calculated density = 1.443 g cm⁻³; space group = P2₁; number of reflections = 1630 of which 1425 were considered independent (R int = 0.0217). Refinement method was full-matrix least-squares on F^2 . The final R -indices were $\{I > 2\sigma(I)\}$ $R1 = 0.0298$, $wR2 = 0.0858$.

15 **EXAMPLE 75: Single-Crystal X-ray Analysis of (1*S*)-18a.**

Monoclinic crystals of the purified (1*S*)-18a were obtained from CH_2Cl_2 /heptane. A representative crystal was selected and a data set was collected at room temperature. Pertinent crystal, data collection and refinement parameters: crystal size, $0.64 \times 0.32 \times 0.18$ mm; cell dimensions, $a = 15.000$ (1) Å, $b = 7.018$ (1) Å, $c = 15.886$ (1) Å, $\alpha = 90^\circ$, $\beta = 99.34$ (1) °, $\gamma = 90^\circ$; formula, $\text{C}_{16}\text{H}_{19}\text{Cl}_2\text{NO}_3$; formula weight = 344.22; volume = 1650.1 (2) Å³; calculated density = 1.386 g cm⁻³; space group = P2(1); number of reflections = 3267 of which 2979 were considered independent (R int = 0.0285). Refinement method was full-matrix least-squares on F^2 . The final R -indices were $\{I > 2\sigma(I)\}$ $R1 = 0.0449$, $wR2 = 0.1236$.

EXAMPLE 76: Tissue sources and preparation.

Brain tissue from adult male and female cynomolgus monkeys (*Macaca fascicularis*) and rhesus monkeys (*Macaca mulatta*) was stored at -85 °C in the primate brain bank at the New England Regional Primate Research Center. We recently cloned the DAT and SERT from both species and found them to have virtually identical protein sequences (Miller, G. M. et al., *Brain Res. Mol. Brain Res.* 2001, 87, 124-143). The caudate-putamen was dissected from coronal slices and yielded 1.4 ± 0.4 g tissue. Membranes were prepared as described previously. Briefly, the caudate-putamen was homogenized in 10 volumes (w/v) of ice-cold Tris.HCl buffer (50 mM, pH 7.4 at 4 °C) and centrifuged at 38,000 x g for 20 min in the cold. The resulting pellet was suspended in 40 volumes of buffer, and the entire procedure was repeated twice. The membrane suspension (25 mg original wet weight of tissue/ml) was diluted to 12 ml/ml for ^{3}H WIN 35,428 or ^{3}H citalopram assay in buffer just before assay and was dispersed with a Brinkmann Polytron homogenizer (setting #5) for 15 sec. All experiments were conducted in triplicate and each experiment was repeated in each of 2 - 3 preparations from individual brains.

EXAMPLE 77: Dopamine transporter assay.

The dopamine transporter was labeled with ^{3}H WIN 35,428 (^{3}H CFT, (1*R*)-2β-carbomethoxy-3β-(4-fluorophenyl)-*N*- ^{3}H methyltropane, 81 - 84 Ci/mmol, DuPont-NEN). The affinity of ^{3}H WIN 35,428 for the dopamine transporter was determined in experiments by incubating tissue with a fixed concentration of ^{3}H WIN 35,428 and a range of concentration of unlabeled WIN 35,428. The assay tubes received, in Tris.HCl buffer (50 mM, pH 7.4 at 0 - 4 °C; NaCl 100 mM), the following constituents at a final assay concentration: WIN35,428, 0.2 ml (1 pM - 100 or 300 nM), ^{3}H WIN 35,428 (0.3 nM); membrane preparation 0.2 mL (4 mg original wet weight of tissue/mL). The 2 h incubation (0 - 4 °C) was initiated by addition of membranes and

terminated by rapid filtration over Whatman GF/B glass fiber filters pre-soaked in 0.1% bovine serum albumin (Sigma Chem. Co.). The filters were washed twice with 5 mL Tris.HCl buffer (50 mM), incubated overnight at 0 - 4 °C in scintillation fluor (Beckman Ready-Value, 5 mL) and radioactivity was measured by liquid scintillation spectrometry (Beckman 1801). Cpm were converted to dpm following determination of counting efficiency (> 45%) of each vial by external standardization.

Total binding was defined as ${}^3\text{H}\text{WIN}$ 35,428 bound in the presence of ineffective concentrations of unlabeled WIN 35,428 (1 or 10 pM). Non-specific binding was defined as ${}^3\text{H}\text{WIN}$ 35,428 bound in the presence of an excess (30 μM) of (-)-cocaine. Specific binding was the difference between the two values. Competition experiments to determine the affinities of other drugs at ${}^3\text{H}\text{WIN}$ 35,428 binding sites were conducted using procedures similar to those outlined above. Stock solutions of water-soluble drugs were dissolved in water or buffer and stock solutions of other drugs were made in a range of ethanol/HCl solutions or other appropriate solvents. Several of the drugs were sonicated to promote solubility. The stock solutions were diluted serially in the assay buffer and added (0.2 mL) to the assay medium as described above. IC₅₀ values were computed by the EBDA computer program and are the means of experiments conducted in triplicate.

EXAMPLE 78: Serotonin transporter assay.

The serotonin transporter was assayed in caudate-putamen membranes using conditions similar to those for the dopamine transporter. The affinity of ${}^3\text{H}\text{citalopram}$ (spec. act.: 82 Ci/mmol, DuPont-NEN) for the serotonin transporter was determined in experiments by incubating tissue with a fixed concentration of ${}^3\text{H}\text{citalopram}$ and a range of concentrations of unlabeled citalopram. The assay tubes received, in Tris.HCl buffer (50 mM, pH 7.4 at 0 - 4 °C; NaCl 100 mM), the following constituents at a final assay concentration: citalopram, 0.2 ml (1 pM - 100 or 300 nM), ${}^3\text{H}\text{citalopram}$ (1 nM);

membrane preparation 0.2 ml (4 mg original wet weight of tissue/mL). The 2 h incubation (0 - 4 °C) was initiated by addition of membranes and terminated by rapid filtration over Whatman GF/B glass fiber filters pre-soaked in 0.1% polyethyleneimine. The filters were washed twice with 5

5 ml Tris.HCl buffer (50 mM), incubated overnight at 0 - 4 °C in scintillation fluor (Beckman Ready-Value, 5 mL) and radioactivity was measured by liquid scintillation spectrometry (Beckman 1801). Cpm were converted to dpm following determination of counting efficiency (> 45%) of each vial by external standardization. Total binding was defined as

10 $\{\text{³H}\}$ citalopram bound in the presence of ineffective concentrations of unlabeled citalopram (1 or 10 pM). Non-specific binding was defined as $\{\text{³H}\}$ citalopram bound in the presence of an excess (10 μM) of fluoxetine. Specific binding was the difference between the two values. Competition experiments to determine the affinities of other drugs at $\{\text{³H}\}$ citalopram 15 binding sites were conducted using procedures similar to those outlined above. IC₅₀ values were computed by the EBDA computer program and are the means of experiments conducted in triplicate.

The present invention has been described in detail, including the preferred embodiments thereof. However, it will be appreciated that 20 those skilled in the art, upon consideration of the present disclosure, may make modifications and/or improvements of this invention and still be within the scope and spirit of this invention as set forth in the following claims.

All references cited are incorporated herein in their entirety by 25 reference.